UNIVERSIDADE DE LISBOA
Faculdade Medicina Veterinária

ESTIMATING THE BURDEN OF DISEASE OF DIETARY EXPOSURE TO CHEMICAL HAZARDS: INORGANIC ARSENIC AS A CASE-STUDY

MAFALDA PATRÍCIO SOLIPA FILIPE

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DISSERTAÇÃO DE MESTRADO EM SEGURANÇA ALIMENTAR

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Estimating the burden of disease of dietary exposure to chemical hazards: inorganic arsenic as a case-study

Abstract

Arsenic is a metalloid or a semi-metal that is widely distributed in the Earth's crust. There are three major groups of arsenic compounds: arsine gas, inorganic and organic arsenic. However inorganic arsenic is considered more toxic than organic arsenic. The general population is exposed to this chemical primarily through consumption of foods and drinking water. Epidemiological studies and case reports of humans have demonstrated that exposure to arsenic and arsenic compounds increases the risk of cancer (e.g.: skin, bladder, kidney, liver, lung, and prostate). Nevertheless, arsenic exposure is more strongly associated to skin, lung, and bladder cancer. In this study, the burden of disease (BoD) caused by dietary exposure to inorganic arsenic in Denmark was estimated using disability adjusted life years (DALY) as health metric. An exposure-based approach was applied with a model of three components: exposure, health-outcome and DALY-module. The lifetime daily exposure to inorganic arsenic through food in the Danish population was estimated to be 0.10 µg/kg bw/day [95% UI: 0.01; 0.33] and 0.08 µg/kg bw/day [95% UI: 0.01; 0.26] for males and females, respectively. Results suggest that the number of cancer cases attributable to foodborne exposure to inorganic arsenic in Denmark is low, with less than one case each year (0.26 cases per year), as is the overall burden of disease, estimated to be 1.8 DALYs. These results can provide a comparison with other estimations of BoD of other foodborne hazards for prioritizing policies. However, this study also shows that all methodological choices and assumptions of a BoD model need to be careful considered when DALYs are interpreted.

Key words: Inorganic arsenic; cancer; DALY; disease burden; food

Estimativa da carga de doença na exposição a perigos químicos através da alimentação: arsénico inorgânico como estudo de caso

Resumo

O arsénico é um metalóide ou um semimetal que é abundantemente distribuído na crosta terrestre. Existem três grupos principais de compostos de arsénico: arsina, arsénico inorgânico e orgânico. No entanto, o arsénico inorgânico é considerado mais tóxico do que orgânico. A população em geral está exposta a este químico principalmente através do consumo de alimentos e de água potável. Estudos epidemiológicos e relatos de casos em seres humanos demonstraram que a exposição ao arsénico e aos seus compostos aumenta o risco de cancro (ex.: pele, bexiga, rins, fígado, pulmões e próstata). Contudo, a exposição ao arsénico esteja mais fortemente associada aos cancros da pele, pulmões e bexiga. Neste estudo o peso da doença causada pela exposição ao arsénico inorgânico através dos alimentos na Dinamarca foi estimada usando os anos de vida ajustados por incapacidade (DALYs) como métrica de saúde. Uma abordagem baseada na exposição foi aplicada com um modelo de três componentes: exposição, resultados de saúde e DALYs. A exposição diária ao arsénico inorgânico através dos alimentos na população dinamarquesa foi estimada como sendo 0.10 µg/kg [95% UI: 0.01; 0.33] peso corporal/dia e 0.08 µg/kg [95% UI: 0.01; 0.26] peso corporal/dia para homens e mulheres, respetivamente. Os resultados sugerem que o número de casos de cancro atribuídos à exposição do arsénico através da alimentação na Dinamarca é baixo, com menos de um caso por ano (0.26 casos por ano) e, com um peso global da doença, estimado em 1,8 DALYs. Estes resultados podem fornecer uma comparação com outras estimativas de peso de doença de outros riscos alimentares para priorizar medidas. No entanto, este estudo também mostra que todas as escolhas metodológicas e pressupostos de um modelo de peso da doença precisam de ser cuidadosamente consideradas quando são interpretados DALYs.

Palavras-Chave: Arsénico inorgânico; cancro; DALY; peso da doença; alimentos

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Abbreviations

As: Arsenic

AS3MT: Arsenite Methyl-Transferase

BCF: Bioconcentration Factor

BAF: Bioacumulation Factor

BCC: Basal Cell Carcinoma

BFDEA: Blackfoot Disease Endemic Area

bw: body weight

COPD: Chronic Obstructive Pulmonary Disease

CSF: Cancer Slope Factor

DALY: Disability Adjusted Life Years

DMA (V): Dimetilarsinic Acid

DW: Disability Weight

EFSA: European Food Safety Authority

EDI: Exposure Dietary Intake

FBD: Foodborne Disease

FERG: Foodborne Disease Burden Epidemiology Reference Group

GBD: Global Burden of Disease

GSH: Glutathione

iAs: Inorganic Arsenic

LE: Life Expectancy

MMA^{V}: Methylarsonic Acid

MMA^{III}: Methylarsonous Acid

ppm: parts per million

SAM: S-Adenosyl Aethyonine

SF: Slope Factor

SD: Standard Deviation

SMR: Standardized Mortality Rate

SqCC: Squamous Cell Carcinoma

UI: Uncertainty Interval

VTEC: Verocytotoxin producing Escherichia Coli

WHO: World Health Organization

YLD: Years Lost due to Disability

YLL: Years of Life Lost

µg/L: microgram per liter

g/day: gram per day

µg/kg: microgram per kilogram

µg/kg bw/day: microgram per kilogram body weight per day

1. Introduction

Foodborne diseases have been an issue for all societies since the beginning of humanity and an important cause of morbidity and mortality. They are the result of ingesting contaminated foodstuffs, and range from diseases caused by a microbial pathogens, parasites, chemical contaminants and bio-toxins (WHO, 2015).

However the full extent and burden of unsafe food, and especially the burden arising from chemicals has been unknown. Estimating the burden of disease due to foodborne chemical hazards is particularly challenging because a) they typically cause chronic diseases that onset a long time after exposure and this is difficult to associate with exposure and, b) lead to a health outcomes that can be caused to various other risk factors.

Arsenic is a chemical that is known to cause cancer, as well as many other serious health problems. Food (e.g.: fish, shellfish, meat, poultry, dairy products, cereals, rice/rice cereal) and drinking water are usually the largest sources (ATSDR, 2007).

Burden of disease is the impact of a health problem as measured by mortality, morbidity and disability. The most commonly used metric to estimate the burden of diseases is the disability adjusted life years (DALYs) (Murray & Lopez, 1996).

The main idea behind the framework of the DALYs is to incorporate both mortality and non-fatal health outcomes into a single measurement unit. This unit is essential to provide a comprehensive and comparable measure for describing the burden of disease and conditions in all countries worldwide (ECDC, 2011; Haagsma, Polinder, & Havelaar, 2011).

For estimating the burden of disease of foodborne of chemicals it is useful to adopt an exposure assessment approach, which requires adequate data on foodborne exposure. It is also important to express the risk due to a chemical exposure as an annual incidence of the given health effect caused by the chemical. For this, it is necessary to measure the exposure to the chemical in the population by combining food consumption data with concentration data of chemicals in food and then link this with a dose response model (WHO, 2006, 2009, 2015).

To address current knowledge gaps, this study was performed with the objective of understanding the impact that chemical hazards present in food have in the population health through the estimation of the burden of disease of dietary exposure to inorganic arsenic.

This project was carried out in Denmark, at the National Food Institute, Technical University of Denmark where, with the support of several researchers, the burden of disease (BoD) caused by dietary exposure to inorganic arsenic was estimated in the Danish population.

2. Literature Review

2.1. Burden of Disease

Foodborne diseases are an important cause of morbidity and mortality worldwide. They are the result of ingesting contaminated foodstuffs and range from diseases caused by microorganisms to those caused by chemical hazards. The most common clinical presentation of foodborne diseases results in gastrointestinal symptoms, but foodborne diseases can also lead to chronic, life-threatening symptoms including neurological, gynecological or immunological disorders as well as multi-organ failure, cancer and death (WHO, 2007).

The burden of disease concept provides a methodological framework to quantify and compare the health of populations using the disability adjusted life years (DALYs): a summary measure of population health that includes the effects of mortality, morbidity (the presence of diseases) and disability (loss of function). Identify the relative magnitude of different health problems and risk factors are the main targets in assessing burden of disease. This insight is significant for medical resource allocation and for targeting and monitoring possible impact of interventions in the food chain (Murray & Lopez, 1996; WHO, 2015).

Burden of disease analyses should provide DALYs estimates based on the overall prevalence or incidence of morbidity and disabilities in the population and for that, detailed knowledge on epidemiology and health effects is needed. However, this is particularly challenging, because epidemiological data on foodborne diseases remain scarce and because of the wide range of causative agents and their health effects and the time between exposure and symptoms (Haagsma et al., 2011).

2.1.2. Global Burden of Disease and Burden of Chemical Foodborne Disease Studies

In 1992, the original Global Burden of Disease (GBD) study was commissioned by the World Bank, where researchers and collaborators from all over the world have produced a comprehensive, consistent and comparable set of estimates of current patterns of the world. This study generated consistent estimates of mortality, incidence, prevalence and disability for 107 diseases and 483 sequelae (non-fatal health consequences related to a disease), by proposing a single metric - the DALYs (Mathers, Ezzati, & Lopez, 2007; Murray & Lopez, 1996).

The World Health Organization (WHO) officially adopted the Burden of Disease and DALY approach and individual technical units and programs within WHO used and further developed the method and built collaborations with external experts to continue to update GBD findings.

In 1998, the WHO created a Disease Burden Unit, which generated GBD estimates for 2000, 2001, and 2002, publishing the estimates in WHO's annual World Health Reports (WHO, 2007).

In September 2006, the World Health Organization (WHO) Department of Food Safety, Zoonoses and Foodborne Diseases (FOS) together with its partners launched the Initiative to Estimate the Global Burden of Foodborne Diseases in order to enable policy-makers and other stakeholders to set appropriate, evidence-based priorities in the area of food safety. This was the first time that an initiative aims to generate estimates of burden of foodborne disease from all causes of microbial, parasitic and chemical origin, and stratify the data by sex, age and WHO region (WHO, 2006).

In 2007, WHO established a Foodborne Disease Burden Epidemiology Reference Group (FERG) as a technical advisory body to engaged in assembling, appraising and reporting on currently existing burden of foodborne disease estimates; conducting epidemiological reviews for mortality, morbidity and disability in each of the major foodborne diseases; providing models for the estimation of foodborne disease burden where data are lacking; developing cause and source attribution models to estimate the proportion of diseases that are foodborne and developing user-friendly tools for burden of foodborne disease studies at country level. The organization established a Steering Group to coordinating and overseeing the burden work as well as several thematic Task Forces (TFs) to advance the work in specific areas including : Enteric Diseases Task Force (EDTF), Parasitic Diseases Task Force (PDTF) and Chemical and Toxins Task Force (CTTF) (WHO, 2007).

The latter Task Force identified groups of chemicals and toxins that are of highest priority in estimating the burden of foodborne disease. The hazards were ranked on: the severity of potential health effects; the prevalence of exposure; and on the availability of data to make burden estimates. The chemicals and toxins that burdens could be estimated were aflatoxin, cyanide in cassava, peanut allergen, dioxin and dioxin-like compounds, methylmercury, lead, arsenic and cadmium. However only the results for aflatoxin, cyanide in cassava, peanut allergen and dioxin were reported by the organization (WHO, 2015).

Other studies on burden of chemical foodborne disease were performed such as Oberoi et al. (2011) study that estimated "The Global Burden of Disease caused by Arsenic in Food" and Jakobsen et al. (2016) study estimated the "Burden of disease of dietary exposure to acrylamide in Denmark".

2.1.3. Disability Adjusted Life Year – DALY

The most commonly used metric to estimate the burden of diseases is the disability adjusted life years (DALYs). This concept was introduced in 1993 by the World Bank and was gained wide adherence after the GBD study in 1996 (Pires, 2014).

The main idea behind the framework of the DALY was to incorporate both mortality and non-fatal health outcomes into a single measurement unit. This unit was essential to provide a comprehensive and comparable tool for describing the burden of disease and conditions in all countries worldwide (Haagsma et al., 2011).

The DALY belongs to the family of health-gap measures that calculate health losses based on the gap between the current health status and some ideal health goal that is defined arbitrarily. In other words, every person is born with a certain number of life years potentially lived in optimal health but people can lose these healthy life years through living with illness and/or through dying before a reference life expectancy. What is measured by the DALY metric are these losses in healthy life years: one DALY represents a loss of one year of life lived in perfect health (Devleesschauwer et al., 2014; Murray & Lopez, 1996)

To calculate total DALYs for a given condition in a population, years of life lost due to premature mortality (YLLs) and years lived with disability of known severity and duration (YLDs) for that condition must each be estimated, and then the total summed (Murray & Lopez, 1996).

Basic formulae:

$$DALY = YLL + YLD$$

The number of years of life lost due to premature mortality (YLL) is the mortality component of DALYs and is calculated by summing the number of all fatal cases due to the health outcomes of a specific disease, each case multiplied by the remaining individual life expectancy at the age of death in years in standard life tables (Murray & Lopez, 1996).

Basic formulae:

$$YLL = \Sigma\, di^* e$$

where *d* is the number of fatal cases due to health outcome *i* in a certain period and *e* is the residual expected individual life span at the age of death.

The number of years lost due to disability (YLD) requires estimation of the incidence of the health condition (disease or injury) and is estimated by multiplying this incidence with the average duration of the condition (to remission or death) and with the disability weight (Dw) that quantifies the equivalent loss of healthy years of life due to living with the health condition or its sequelae (Mathers, Vos, Stevenson, & Begg, 1999).

Basic formulae:

$$YLD = \Sigma\, (di^* ti^* dwi)$$

where *d* is the number of cases with health outcome *i*, *t* is the duration of the health outcome (the average number of days of illness or injury consequences) and *dw* the disability weight assigned to health outcome *i*

The figure 1 represents a theoretical example of an individual that was born in a perfect state of health (0) during 20 years, when something happens (a disease or an injurie) which leads to a decrease of quality of life (40%). The person lives the new health state for other 40 years, at which point dies prematurely. The burden associated of this disease for this individual was calculated by summing the years of life lost due to living with disability (YLD) with the years of life lost to premature death (1), when compared with the life expectancy in the population (YLL)

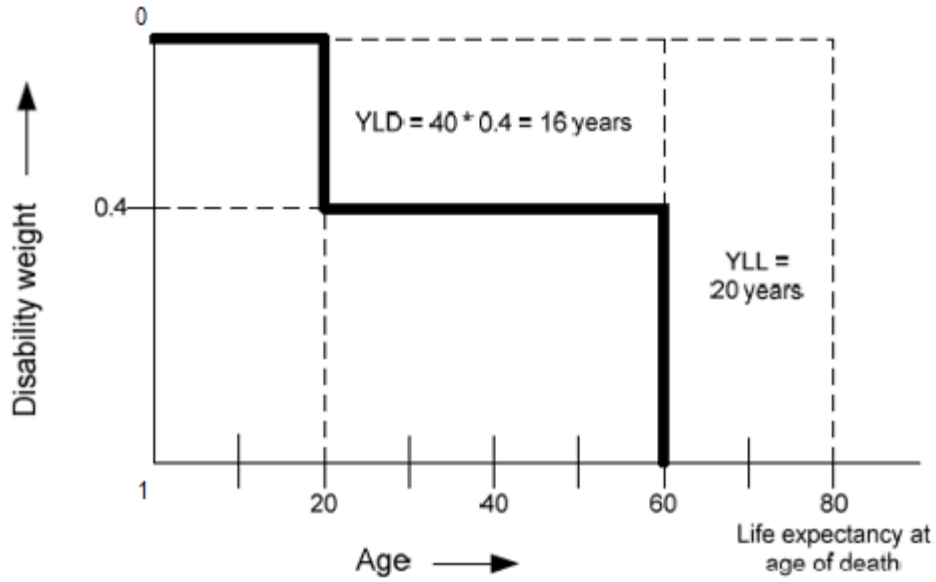

Figure 1 – A theoretical example of DALYs, adapted from Pires (2004).

2.1.3.1. Incidence *versus* Prevalence Approach

DALYs, and more specifically their YLD component, may be calculated from an incidence or a prevalence perspective. While incidence-based YLDs are defined as the product of the number of incident cases and the duration and disability weight (Dw), the prevalence-based YLDs are defined as the product of the number of prevalent cases and the corresponding Dw.(WHO, 2015).

Time lost due to premature mortality is a function of death rates and the duration of life lost due to a death at each age. Because death rates are incidence rates, using an incidence approach is deemed the most appropriate. Furthermore, this approach is more sensitive to current epidemiological trends, is consistent with the estimations of YLLs, which by definition follows an incidence-based approach and will reflect the impact of health interventions more rapidly (Murray, 1994).

2.1.3.2. Incidence data

The starting point for the burden of disease calculations is to determine the number of new cases of a particular disease or its sequelae. Most studies derived numbers of incident cases directly from disease registers, routine databases or epidemiological studies. However only data on the registered cases and in some cases supplementary data are available from health surveys or epidemiological studies which leads to considered that registered incidence data do not cover all disease cases in the population. This lack on the incidence data can leads to cases of foodborne diseases underreported or underdiagnosed (ECDC, 2011).

Underreporting refers to cases that have sought medical advice but are not correctly diagnosed, classified, notified, or disseminated to surveillance authority, moreover diseases may not be attributed to the agent, because the association between the agent and health outcome is not clear due to time between exposure to the agent and health effects and because the health effects can arise from an intricate combination of factors, including exposure to the agent. Underdiagnosing refers to cases in the community that do not seek medical advice. Health outcomes caused by foodborne disease vary from mild to very severe and registered diseases often represent only a tip of the ice berg of all disease and the (Salomon et al., 2012).

While foodborne pathogens mostly cause middle to moderate gastroenteritis, in case of chemicals, they can cause very severe diseases (such as cancer) and connecting exposure to chemicals and health effects is difficult because the health effects of chemicals may not be observed for years following and data linking dose exposure to effect (e.g.: dose-response) are often lacking (Gibb et al., 2015).

Figure 2 represents the occurrence and detection of health impacts from chemicals.

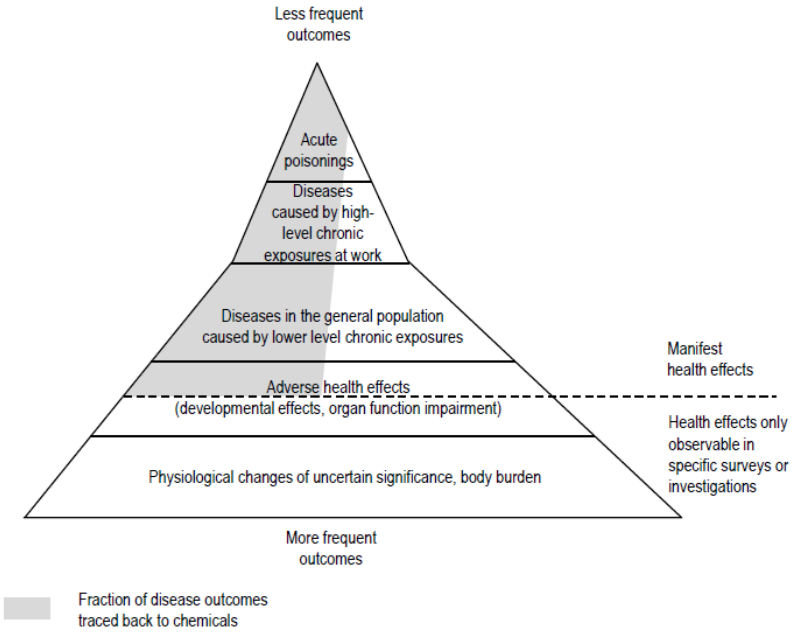

Figure 2- Occurrence and detection of health impacts from chemicals, adapted from Prüss-Ustün et al. (2011)

2.1.3.3. Data Sources

2.1.3.3.1. Laboratory surveillance data

Laboratory surveillance can be subdivided into passive and active surveillance. Laboratory surveillance data may include data from hospitalizations, general practitioner cases and deaths attributable to the agent (ECDC, 2011).

2.1.3.3.2. Community based study data

Community based study data includes data from population-based surveys and serological surveys. Population-based surveys are used to assess disease in a community where the disease refers to the cases that fulfil a particular case definition. The cases included in the survey may either be a randomly chosen sample or a cohort followed over a certain period of time. Serological surveys may also be used to assess incidence in a community where serological survey serum samples are collected from a representative sample of the population and are then tested on the presence of antibodies against of infectious diseases or the presence of chemical agents (ECDC, 2011).

2.1.3.4. Disability Weights (Dw)

The reference state for good or ideal health is defined as a health state where the individual has no pathological processes (disease or disease precursors), no mental health problems, no injuries, no impairments resulting from congenital, disease or injury causes; and no functional limitations resulting from current or former health problems or impairments. Thus, disability weights and years lost due to disability (YLD) can be referred as shorthand terms for health state preferences and years of healthy life lost due to time lived in states other than the reference state of good health, respectively (Mathers et al., 1999).

Ideally, the disability weights used to estimate a burden should reflect the values measured in the populations studied. However, disability weights are not usually available at the national level and have to be determined using different methods that involve asking people to compare various health states. The weights reflect the values for the general population (ECDC, 2011).

The disability weights used in DALYs calculations quantify societal preferences for different health states. They range between zero (equivalent to full health) and one (equivalent to death) (Salomon et al., 2012).

These weights do not represent the lived experience of any disability or health state, or imply any societal value of the person in a disability or health state (e.g.: a weight for paraplegia of 0.57 does not mean that a person in this health state is ‘half dead’ or that they experience their life as halfway between life and death, neither that society values them as a person less than anyone else. It means that, on average, society judges a year with, for example, blindness (weight 0.43) to be preferable to a year with paraplegia (weight 0.57), and a year

with paraplegia to be preferable to a year with, for example, unremitting unipolar major depression (weight 0.76)) (Mathers et al., 1999).

Various studies have estimated disability weights that may be used to calculate burden of disease, such as the GBD disability weights (C. Murray & Lopez, 1996), the Dutch Disability Weights (Stouhard, Essink-Bot, & Bonsel, 2000) and The Burden of Disease and Injury In Australia (Mathers et al., 1999).

2.1.3.5. Duration and Severity of Health States

Information about duration and severity of health states can be directly available from health facility data, disease registers or epidemiological studies. For several diseases, information on duration may not available and duration may be derived from expert opinion or modelled from estimates of prevalence, remission, case fatality rates and background mortality (Devleesschauwer et al., 2015).

Durations of health states for chronic diseases (e.g.: cancer) are usually measured in years. Disability weights are then defined per life year lived with this disability. For conditions lasting more than one year the disability weights will be multiplied by the duration in years to obtain the total burden (ECDC, 2011).

In case of cancer, Mathers et al. (1999) developed a model to estimate disability weights for each cancer considering the cancer stages and sequelae (Figure 2). They considered five stages: diagnosis and primary therapy, the state after intentionally curative primary therapy, in remission, disseminated carcinoma and terminal phase. While the durations of the initial treatment, disseminated and terminal stages were specified separately for each cancer site, the duration of the remission stage was taken as the total mean survival time less the sum of the durations of the initial treatment, disseminated and terminal stages. For the state after intentionally curative primary therapy, the duration was taken as five years less the duration of the initial treatment stage. For most cancers, the proportion cured for the cancer was taken as the proportion surviving five years.

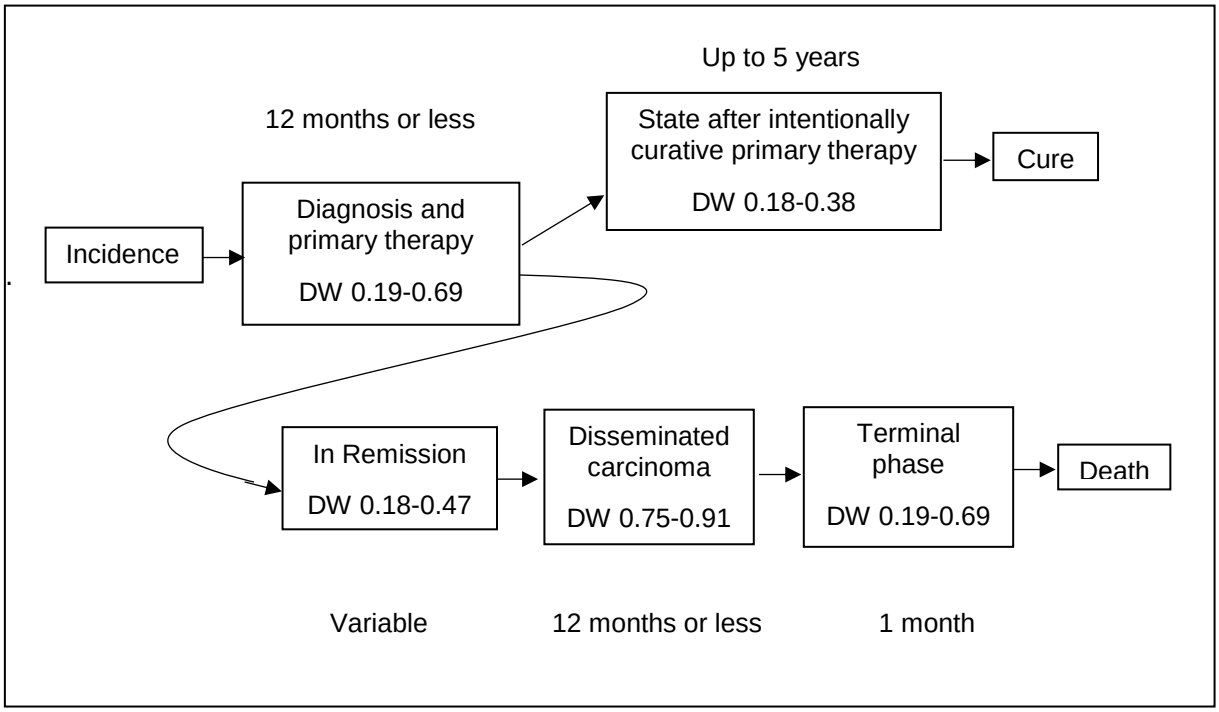

Figure 3 - General model for cancer YLD estimation, including disability weight (DW) and duration ranges adapted from Mathers et al. (1999)

2.1.3.6. Number of Fatal Cases/Non-Fatal Cases

The calculation of mortality burden is straightforward, and the precision of the estimates of YLL depends almost entirely on the quality of data on underlying causes of death. Most industrialized countries register the number of fatal cases, the age and cause of death in vital registrations. Some countries also have a website on which general information about their vital registration system is published (Mathers et al., 2001).

The number of disease and cause-specific fatalities from diseases with various causes it can be estimated by multiplying the absolute number of fatal cases obtained from disease-specific registers by an attributable fraction obtained from the literature. In the case of fatal cases, the mortality is often not attributed to the underlying communicable disease and for these cases is necessary to estimate what fraction of the conditions registered as cause of death can be attributed to a communicable disease. However, for some conditions and countries, estimates of attributable fractions are available. Regarding to non-fatal cases, depending on the communicable disease, incidences have to be estimated for a varying number of non-fatal outcomes or can be obtained by using the incidence of one outcome (ECDC, 2011).

2.1.3.7. Life Expectancy

In order to measure the difference between a population's actual health status and an 'ideal' or reference status, the 'ideal' or reference status has to be specified and for that is necessary to regard life expectancy (Mathers et al., 2001).

The duration component of the YLDs is defined as the average observed duration until remission or death and when this duration is lifelong, the country-specific life expectancy should be used. On the other hand, the time component of the YLLs is defined as the ideal residual life expectancy a person would have if the world would be free from disease and provide maximal access to health care (United Nations, 2013).

2.1.3.8. Presenting DALYs

DALYs can be expressed as an absolute number, giving an idea of the total population burden. They can also be expressed relative to the population (e.g.: as the number of DALYs per 100,000 inhabitants) which enables a direct comparison of the burden suffered by different populations. DALYs may also be expressed relative to the number of cases which allows comparisons of the impact of diseases at the patient-level, instead of at the population level (ECDC, 2011).

2.1.4. Quantitative Risk Assessment

Risk assessment of chemicals can be performed to evaluate past, current and even future exposures to any chemical found in air, soil, water, food or consumer products however are often limited by a lack of complete information. Chemical risk assessments rely on scientific understanding of the behavior, exposure, dose and toxicity and depends on several factors such as the amount of a chemical present in an environmental medium, food and/or a product, the amount of contact (exposure) a person has with the chemical and the toxicity (WHO, 2010).

2.1.4.1. Exposure Assessment

Exposure data are used to calculate exposure levels of a population that are used to calculate the proportion of the population that is affected based on dose-response information. This proportion is then used to calculate prevalence or incidence in the population, In the case of chemicals, the exposure data is the key to estimate the incidence of a health outcome associated to a chemical exposure due to the complications to link chemicals to their health outcomes (Mathers et al., 2001).

Exposure assessment involves estimating the intensity, frequency, and duration of human exposures to a toxic agent. Regarding to chemicals, exposure depends on the concentration of the chemical in individual foods and the rate of consumption of these food items. So, the dietary exposure assessments combines food consumption data with data on the concentration of chemicals in food. The resulting dietary exposure estimate is then compared with the relevant toxicological or nutritional reference value for the food chemical of concern. (WHO, 2009).

2.1.4.2. Dose-response Assessment

A dose-response relationship describes how the likelihood and severity of adverse health effects (the responses) are related to the amount and condition of exposure to an agent (the dose provided). Typically, as the dose increases, the measured response also increases. The shape of the dose-response relationship depends on the agent, the kind of response (tumor, incidence of disease, death, etc) and the experimental subject (human, animal) in question (US EPA, 2005).

Dose-response assessment involves quantitative evaluation of the toxicity information in order to characterize the relationship between the dose of the contaminant and the probability of adverse health effects in the exposed population. This relationship is characterized to derive quantitative toxicity values (i.e., cancer slope factors or reference doses) (Wignall et al., 2014).

When the health effect is cancer, it is traditionally assumed that there is no threshold of exposure to a carcinogen below which there is no observable adverse effect and the cancer potency factors are estimated from the slope of the dose– response relationship, which is assumed to be linear, between doses of the carcinogen and cancer incidence in a population (Abt, Rodricks, Levy, Zeise, & Burke, 2010).

A slope factor is an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent by ingestion. This estimate, usually expressed in units of proportion of a population affected per mg of substance/kg body weight-day, provides a probability of a response per unit intake of a chemical over a lifetime and usually is reserved for use in the low-dose region of the dose-response relationship (USEPA, 1988).

2.2. Arsenic

2.2.1. Physical and Chemical Properties

Arsenic is a metalloid or a semi-metal that is widely distributed in the Earth's crust and that occurs naturally in soil, water, living organisms and in many kinds of rock, especially in minerals and ores that contain copper or lead. Elemental arsenic normally occurs as the α-crystalline metallic form, which is a steel gray and brittle solid. However other allotropic forms of arsenic may also exist. (ATSDR, 2007; IARC, 2012; WHO, 2011).

When is combined with other elements such as carbon and hydrogen is referred to as organic arsenic and when is combined with oxygen, chlorine, and sulfur is considered inorganic arsenic, generally more toxic than the organic form (ATSDR, 2007).

Both inorganic and organic forms are found in different valence or oxidation states. The valence states of arsenic are As(0) (metalloid arsenic, 0 oxidation state), As(III) (trivalent, 3 oxidation state), As(V) (pentavalent, 5 oxidation state) and Arsine Gas (-3 oxidation state). Interchanges of valence state may occur in aqueous solutions, depending on the pH (

oxygenated media and higher pH favor the pentavalent form, while reducing and/acid media favor trivalent state) and on the presence of other substances which can be reduced or oxidized (ATSDR, 2007; Hughes, Beck, Chen, Lewis, & Thomas, 2011).

Trivalent inorganic arsenic compounds are arsenic trioxide, sodium arsenite and arsenic trichloride. Pentavalent inorganic compounds include arsenic pentoxide, arsenic acid and arsenates. Common organic arsenic compounds are arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid) and arsenobetaine (Nordberg, Fowler, Nordberg, & Friberg, 2007).

Arsenic trioxide, As_2O_3, is only sparingly soluble in water and other solvent which do not promote chemical transformation. The pentavalent arsenic pentoxide, As_2O_5, has high solubility in water forming the strong oxidizing arsenic acid H_3AsO_4. In soils arsenic compounds tend to form insoluble complexes (EPA, 1985).

2.2.2. Natural Sources

Arsenic appears naturally in the form of sulfides in association with the sulfides of ores of silver, lead, copper, nickel, antimony, cobalt and iron, which leads to elevated levels in soils in many mineralized areas. Arsenic is also naturally released to the atmosphere principally through volcanic activity, with minor contributions by exudates from vegetation and windblown dusts (ATSDR, 2007; WHO, 2001).

Arsenic concentrations in uncontaminated soil are generally in the range 0.2 to 40 mg/kg. However, depending on the geographic regions, concentrations can range between 100 to 2500 mg/kg near arseniferous deposits and in mineralized zones containing gold, silver, and sulfides of lead and zinc (Diaz-Barriga et al., 1993; Eisler, 1994; Jones, 2007).

Because surface and ground waters are often in contact with ores or tailings, arsenic may also be present at high levels in rivers and lakes (Jones, 2007).

Concentrations of arsenic in open ocean can range between 1–2 µg/litre. In unpolluted surface water and groundwater the concentrations of arsenic can range between 1 and 10 µg/litre. However in areas of sulfide mineralization the concentrations of arsenic in surface water and groundwater can be found up to 100–5000 µg/litre (Fordyce, Williams, Paijitprapapon, & Charoenchaisri, 1995; Welch, Westjohn, Helsel, & Wanty, 2000).

Marine organisms, seafood and in some edible algae contain naturally high concentrations of arsenic however in the harmless organic form (arsenobetaine or arsenosugars). Inorganic arsenic (both As(V) and As(III)) and single methylated arsenic species (methylarsonate, methylarsenite and dimethylarsinate) are the predominant forms in terrestrial plants that accumulate arsenic from the soil or from airborne arsenic absorption (EPA, 1982; Francesconi, 2005).

Arsenic can build up (bioaccumulate) in the bodies of aquatic organisms depending on several factors as environmental setting (marine, estuarine, freshwater), organism type (fish,

invertebrate), trophic status within the aquatic food chain, exposure concentrations, and route of uptake (Williams, Schoof, & Yager, 2006).

The major bioaccumulation transfer is between water and algae, at the base of the food chain and this has a strong impact on the concentration in fish. Bioaccumulation data for various fish and invertebrate species analyzed by shown bioconcentration factor (BCF) values between 0.048 and 1.390 (EPA, 2003). From 12 studies of arsenic accumulation in freshwater fish, Williams et al. (2006) reported that Bioconcentration factor (BCF) or Bioaccumulation (BAF) values from ranged from 0.1 to 3.091. They also concluded that bioaccumulation factor (BAF) values are not constant across arsenic concentrations in water. Other study of the factors affecting bioaccumulation of arsenic reported that some species (mainly marine algae and shellfish) tend to bioconcentrate arsenic but does not biomagnify through the food chain (Mason, Laporte, & Andres, 2000).

2.2.3. Anthropogenic Sources

Arsenic is released in the environment through a large variety of man-made sources. It was estimated that anthropogenic emissions are three times higher than natural sources emissions (ATSDR, 2007).

Arsenic is used as an active component of antifungal wood preservatives, in the production of agricultural chemicals (concentrations can vary between countries, depending on the restrictions), in the pharmaceutical and glass industries, in the manufacture of sheep-dips, leather preservatives and poisonous baits. Arsanilic acid and its derivatives 4-aminophenylarsonic and 3-nitro-4-hydroxyphenylarsonic acids are, in some countries, added to cattle and poultry feed at a concentration of 25–45 mg/kg for use as growth-stimulating agents (ATSDR, 2007; EPA, 1985).

Concentrations in ambient air can reach several hundred nanograms per cubic meter in some cities and exceed 1000 ng/m^3 near nonferrous metal smelters and some power plants, depending on the arsenic content in the coal that is burnt. Generally, in most urban/suburban areas, arsenic occurs mainly in the form of a mixture of inorganic arsenic in the tri- and pentavalent states. Methylated arsenic can be found in areas where this form is used agriculturally, or where biotic transformation can occur. (EPA, 1985; WHO, 2001)

2.2.4. Transportation and Biotransformation

Most anthropogenic arsenic emitted to the atmosphere arises from high temperature processes and occurs as fine particles that are transported by wind and air currents until they are returned to earth by wet or dry deposition. Arsenic that falling on soils can be transported into groundwater or surface water and then the transportation follows to sediments into biofilm and lastly into invertebrates and fish (Eisler, 1994; Farag, Woodward, Goldstein, Brumbaugh, & Meyer, 1998; Pacyna, 1987).

Such cycling is made by chemical and biological transformations: redox transformation between arsenite and arsenate, the reduction and methylation of arsenic, and the biosynthesis of organoarsenic compounds. Being the biomethylation and bioreduction the most important transformations because allow the production of organometallic species that are sufficiently stable to be mobile in air and water (WHO, 2001).

In water, the methylation of inorganic arsenic to methyl- and dimethylarsenic acids is associated with biological activity (e.g.: via sedimentary bacteria and suspended marine algae). Some marine organisms have also been shown to transform inorganic arsenic into arsenobetaine, arsenocholine and arsoniumphospholipids. However, in soils this processes of methylation and reduction occur with a limited extend. In atmosphere or in aerated surfaces water, trivalent arsenic can undergo oxidation to the pentavalent form, while pentavalent arsenic can be reduced to the trivalent form (EPA, 1985; WHO, 2001).

2.2.5. Population Exposure

Arsenic is widely distributed and human exposure is inevitable. Exposure to arsenic may include exposure to the more toxic inorganic forms of arsenic, organic forms of arsenic, or both (ATSDR, 2007).

Inhalation of arsenic from ambient air is usually the minor source of arsenic exposure (0.4–0.6 µg/day) to a person who breathes 20 m^3/day of air containing 20–30 ng/m^3. However, smokers may be exposed to arsenic by inhalation of mainstream smoke (EPA, 1984).

Occupational exposure can be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing and arsenical pesticide production and application (ATSDR, 2007).

Drinking water can be a significant source of arsenic exposure. Estimates about 5 µg/day of arsenic intake for typical adults drinking 2 L of water per day average was reported, however intake may vary and can be higher (10–100 µg/day) in geographical areas with high levels of arsenic in soil or groundwater (EPA, 1994).

Because arsenic is present in soil, water, air, plants and all living organisms, finding this chemical in foods is not unexpected. Arsenic present in food usually describe the content of total arsenic (e.g.: the sum of all arsenic species). However information about the type of arsenic is increasingly important because different foods can contain different types of arsenic species, and because these species have different toxicity (from a toxicological point of view, the amount of inorganic arsenic is considered the most important) (JECFA, 2011).

The European Commission Scientific Cooperation project calculated a mean daily dietary exposure between 37 and 66 µg to total arsenic in the adult population in three European countries and estimated seafood contribution in excess of 50 % (SCOOP, 2004).

The United States Food and Drug Administration (FDA) conducted a Total Dietary Study (1991-1996) where concluded that the highest concentrations were found in seafood,

followed by rice/rice cereal, mushrooms, and poultry. The greatest dietary contribution to total arsenic was seafood (76–96%) for all age groups, except infants. For infants, seafood and rice products contributed 42 and 31%, respectively from 11.7 to 280 µg/day. It was also assumed that 10% of the total arsenic in seafood was inorganic and that 100% of the arsenic in all other foods was inorganic, so the average daily exposure of inorganic arsenic was estimated to range from 1.3 µg in infants to 12.5 µg in 60-65-year-old men (Tao, & Bolger, 1998).

In the United States and Canada was reported that the estimated daily dietary intake of inorganic arsenic for various age groups ranged from 8.3 to 14 µg/day and from 4.8 to 12.7 µg/day for infants and for 60-65 years - old man, respectively (Yost, Schoof, & Aucoin, 1998). Rice may has a high dietary contribution of inorganic arsenic exposure (Meacher et al., 2002; Meliker, Franzblau, Slotnick, & Nriagu, 2006; Tsuji, Yost, Barraj, Scrafford, & Mink, 2007). Dietary exposure to inorganic arsenic from rice was calculated for typical adult European as being 2 µg/kg b.w. per day (Jorhem et al., 2008).

The mean daily dietary exposure for inorganic arsenic was estimated for children (1-6 years of age) to be 3.2 µg, with a range of 1.6-6.2 µg for the 10^{th} and 95^{th} percentiles and inorganic arsenic exposure was predominantly contributed by grain and grain products, fruits and fruit juices, rice and rice products, and milk (Yost et al., 2004).

2.2.6. Inorganic Arsenic Levels in Food

Because food products of terrestrial origin generally contain low concentrations of total arsenic and consequently their inorganic arsenic content is also low. However, rice appears to be an exception because it contains significant amounts of inorganic arsenic with concentrations between 0.1-0.4 mg arsenic/kg dry mass (Sun et al., 2008). In a Swedish study, the concentrations of inorganic arsenic in long grain brown rice, parboiled white rice and white rice averaged 0.110 mg/kg (Jorhem et al., 2008) and in a Spanish study, it was evaluated the inorganic arsenic level (0.027 to 0.253 mg/kg) in raw rice originating from either Europe or Asian (Torres-Escribano, Leal, Vélez, & Montoro, 2008). In raw rice, flour, grape juice and cocked spinach, inorganic arsenic concentrations were 0.074 mg/kg, 0.011 mg/kg, 0.009 mg/kg and 0.006 mg/kg, respectively (Schoof, Yost, Eickhoff, & Crecelius, 1999).

Fish and other seafood usually contain high total arsenic, however their levels of inorganic arsenic are low. Concentrations of inorganic arsenic present in Atlantic cod analyzed were <0.001 mg/kg, in shrimp, concentrations of inorganic arsenic were <0.001 mg/kg and in crustaceans and bivalves concentrations ranged from 0.001 to 4.5 mg/kg, even in fish or seafood with high concentrations of total arsenic (Sloth & Julshamn, 2008; Sloth, Larsen, & Julshamn, 2005). A French study looked at arsenic speciation level and reported concentrations of inorganic arsenic between 0.068 and 0.073 mg/kg in bottom dwelling fish

species (Sirot, Guérin, Volatier, & Leblanc, 2009). Schoof et al (1999) also reported concentrations of inorganic arsenic less than 0.001 to 0.002 mg/kg in freshwater and marine fish.

2.2.7. Toxicokinetics

2.2.7.1. Absorption

Inorganic arsenic has a complex metabolism and is readily absorbed through the gastrointestinal tract. However, the absorption depends of several factors such as the solubility of the arsenical compounds, the presence of other food constituents and nutrients in the gastrointestinal tract and on the food matrix itself (WHO, 2000).

Several studies in rats and mice and in humans indicate that arsenite and arsenate present in drinking water are rapidly and nearly completely (about 95%) absorbed after ingestion (ATSDR, 2007a). A study performed in swine revealed that whereas the bioavailability of inorganic arsenic present in mung beans the absorption was almost 100 % however for lettuce and chard, this percentage was only 50%, which leads to suggest an influence of the non-digestible polysaccharide component of the vegetable on the gastrointestinal absorption of arsenic (E. Smith, Juhasz, & Weber, 2009). In a study performed in volunteers who ingested a single oral dose of arsenic (500 µg) either methylarsonate or dimethylarsinate the amount of arsenic in urine after four days represented 78 and 75% of the ingested dose respectively, suggesting a gastrointestinal absorption >75% for pentavalent organoarsenicals (Buchet, Lauwerys, & Roels, 1981).

2.2.7.2. Distribution

In the bloodstream, arsenic is distributed between the plasma and the erythrocytes, in which it is bound to the globin of hemoglobin. The relative amounts depend on the valence and dose of arsenic administered as well as the species of animal. In most species, residue levels are elevated in liver, kidney, spleen and lung. Although, several weeks later, arsenic can be translocated to hair, nails and skin because of the high concentration of sulfur-containing proteins in these tissues (WHO, 2000).

Residual levels tended to be higher for arsenite than arsenate. In a study, tissue distributions for inorganic arsenic and its methylated metabolites were accessed in female mice exposed to arsenic (as arsenate) in their drinking water for 12 weeks and it was observed that total tissue arsenic accumulation (measured as the sum of inorganic arsenic, methylarsonate and dimethylarsinate) was greatest in kidney > lung > urinary bladder > skin > blood > liver. The predominant metabolite in the kidney was methylarsonate, whereas dimethylarsinate was the predominant metabolite in the lung (Kenyon et al., 2008).

2.2.7.3. Metabolism

In mammalian species (including humans), the inorganic arsenicals are biotransformed and excreted mainly as their metabolites. There are two main types of reactions: (1) reduction of pentavalent to trivalent arsenic; (2) oxidative methylation reactions in which trivalent forms of arsenic are sequentially methylated to form mono-, di- and trimethylated products using S-adenosyl methionine (SAM) as the methyl donor and glutathione (GSH) as an essential co-factor (WHO, 2001)

Arsenate enters the cell and then can be transformed enzymatically (about 50-70 %) to the more reactive arsenite. Arsenite undergoes oxidative methylation in the liver and then catalized by arsenic- methyltransferase, resulting in the formation of methylarsonate. The pentavalent arsenic methylarsonate is then reduced to the trivalent form in methylarsonite (Aposhian, Zakharyan, Avram, Sampayo-reyes, & Wollenberg, 2004). Formation of the pentavalent methylated arsenic metabolites can be regarded as detoxification and production of trivalent methylarsonates is considered bioactivation. This latter process may contribute to the toxicity of trivalent arsenic (Csanaky, Németi, & Gregus, 2003).

A study performed in rodents showed that dimethylarsinate can be more methylated and excreted as trimethylarsine (trivalent form). However, trimethylarsine can only be found in humans who had ingested high dose of dimethylarsinate (Cohen, Arnold, Lewis, & Beck, 2006). The major site of the methylation of arsenic is the liver because of its mass and the first pass effect of ingested arsenic (Vahter, 2002).

Trivalent methylated arsenic species are formed before the respective end products of pentavalent species. Arsenite reacts with glutathione, becoming arsenic triglutathione. Arsenic triglutathione is then methylated by arsenic-methyltransferase, resulting in monomethylarsenic diglutathione, which is further methylated by arsenic-methyltransferase to dimethylarsenic glutathione or it becomes methylarsonite after reacting with glutathione (Hayakawa, Kobayashi, & Cui, 2005).

Arsenobetaine is not metabolized in humans and is excreted unchanged in urine (Ma & Le, 1998), arsenosugars are biotransformed mainly to dimethylarsinate, the same metabolite produced from ingested inorganic arsenic (Francesconi & Mckenzie, 2002; Ma & Le, 1998).

2.2.7.4. Excretion

Arsenic and metabolites are excreted in urine and bile. Studies have shown that rats tend to excrete preferentially into bile, although in most mammalian species and humans the major rout of excretion is via urine, being dimethylarsinate the primary urinary metabolite. Humans excrete appreciable amounts of methylarsonate in urine, however it can differ and this variation ca be assumed as being a reflect of arsenic methylation efficiency, with a typical profile of urinary arsenic metabolites consisting of 10-30% inorganic arsenic, 10-20 % methylarsonate and 60-70% dimethylarsinate. Urinary dimethylarsinate percentage can also

be an indicator of methylation efficiency. (Schuhmacher-Wolz, Dieter, Klein, & Schneider, 2009).

2.2.8. Toxicity

Toxicity depends on several factors such as physical state, gas, solution or powder particle size, rate of absorption into cells, rate of elimination, nature of chemical substituents in the toxic compound and the pre-existing state of the patient. Arsenic can occurs in two oxidation states: a trivalent form, arsenite (As_2O_3; As^{III}) and a pentavalent form, arsenate (As_2O_5; As^{V}), being As^{III} 60 times more toxic than As^{V} (Cobo & Castiñera, 1997; Vega et al., 2001).

Arsenic toxicity inactivates up to 200 enzyme involved in cellular energy pathways and DNA replication and repair. Arsenic also exerts its toxicity by generating reactive oxygen intermediates during their redox cycling and metabolic activation processes that cause lipid peroxidation and DNA damage (Cobo & Castiñera, 1997).

2.2.8.1. Mechanism of Pentavalent Arsenic Toxicity

Arsenate can replace phosphate in many biochemical reactions due to their similar structure and properties. For example, arsenate reacts *in vitro* with glucose and gluconate to form glucose-6-arsenate and 6-arsenogluconate, respectively. These compounds resemble glucose-6- phosphate and 6-phosphogluconate, respectively (Gresser, 1981). Arsenate can also replace phosphate in the sodium pump and the anion can exchange the transport system of the human red blood cell (Kenneys & Kaplans, 1988). Depletion of ATP by arsenate has also been observed in cellular systems. ATP levels are reduced in human after exposure (0.01–10 mM) to arsenate (Winski et al., 1998).

2.2.8.2. Mechanism of Trivalent Arsenic Toxicity

Trivalent arsenic, especially, binds thiol or sulfhydryl groups in tissue proteins of the liver, lungs, kidney, spleen, gastrointestinal mucosa, and keratin-rich tissues (skin, hair, and nails) (Cobo & Castiñera, 1997).

Methylated trivalent arsenicals such as monomethylarsonous acid MMA^{III} are potent inhibitors of glutathione (GSH) reductase and thioredoxin reductase. The inhibition is may be due to the interaction of trivalent arsenic with critical thiol groups in these molecules. While inhibition of these enzymes may alter cellular redox status which eventually leads to cytotoxicity, the binding of trivalent arsenic to these critical thiol groups may inhibit important biochemical events which could lead to toxicity (Hu, Su, & Snow, 1998; Lin, Cullen, & Thomas, 1999; Styblo, Serves, Cullen, & Thomas, 1997).

Arsenite also inhibits pyruvate dehydrogenase (PDH) (Hu et al., 1998; Szinicz & Forth, 1988). However monomethylarsonous acid MMA^{III} is considered more potent inhibitor of PDH than arsenite (Petrick, Jagadish, Mash, & Aposhian, 2001). PDH oxidizes pyruvate to acetyl–

CoA, a precursor to intermediates of the citric acid cycle. The citric acid cycle degrades the intermediates, and this provides reducing equivalents to the electron transport system for ATP production. Inhibition of PDH may ultimately lead to decreased production of ATP. Also intermediates of the citric acid cycle can be used in gluconeogenesis. Inhibition of PDH may explain in part the depletion of carbohydrates (Reichl, Szinicz, Kreppel, & Forth, 1988; Szinicz & Forth, 1988).

2.2.8.3. Oxidative Stress

Oxidative stress occurs when reactive oxygen species are generated and react with cellular constituents such as thiols and lipids. Depletion of GSH by oxidants, for example, may alter the redox status of the cell and present a stressful and toxic situation (Hughes, 2002).

Results of both *in vivo* and *in vitro* studies of arsenic-exposed humans and animals arsenic-exposed humans and animals can leads to a possible involvement of increased lipid peroxidation, superoxide production, hydroxyl radical formation, blood non-protein sulfhydrals, and/or oxidant-induced DNA damage (Arrigo, 1999; Keyse & Tyrrell, 1989; S. X. Liu, Athar, Lippai, Waldren, & Hei, 2001; Powis, Debbie, & Coon, 2000; Razo, Quintanilla-vega, Brambila-colombres, & Caldero, 2001; Styblo et al., 1997). Chronic low-dose arsenic alters genes and proteins that are associated with oxidative stress and inflammation (ATSDR, 2007).

Oxidative stress theory for arsenic carcinogenicity can be partially explained by its ability to cause cancer at high rates in the lung, bladder and skin (Yamanaka & Okada, 1994).

2.2.8.4. Genotoxicity

Collectively, *in vitro* and *in vivo* genotoxicity studies have demonstrated that arsenics cause single strand breaks, formation of apurinic/apyrimidinic sites, DNA base and oxidative base damage, DNA-protein crosslinks, chromosomal aberrations, aneuploidy, sister chromatid exchanges, and micronuclei (Brown, Kitchin, & George, 1997; Jha, Noditi, Nilsson, & Natarajan, 1992; Kochhar, Howard, Hoffman, & Brammer- Carleton, 1996; Li & Rossman, 1991; Tice, Yager, Andrews, & Crecelius, 1997; Tinwell, Stephens, & Ashby, 1991; Yamanaka, Hayashi, Kato, Hasegawa, & Okada, 1995).

2.2.8.5. Promotion of Carcinogenesis

Increased concentrations of growth factors can lead to cell proliferation and eventual promotion of carcinogenesis. Altered growth factors, cell proliferation, and promotion of carcinogenesis have all been demonstrated in one or more systems exposed to arsenics. Altered growth factors and mitogenesis were noted in human keratinocytes (Germolec et al., 1996). Cell proliferation was demonstrated in human keratinocytes and intact human skin and rodent bladder cells (Brown & Kitchin, 1996; Cohen & Arnold, 2008; Germolec et al.,

1997; Razo et al., 2001; Trouba, Wauson, Vorce, & Pharmacol, 2000; Wanibuchi et al., 1996). Promotion of carcinogenesis was noted in rat bladder, kidney, liver, and thyroid, and mouse skin and lung (Seike et al., 2002).

2.2.9. Health Effects

The immediate symptoms of oral exposure to inorganic arsenic, both after acute high-dose exposure and after repeated exposure to lower doses, include nausea, vomiting, and diarrhea (WHO, 2016).

The first symptoms of long-term exposure to high levels of inorganic arsenic (e.g. through drinking water and food) are usually observed in the skin and include hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. Other symptoms include peripheral vascular effects, including cyanosis, gangrene, “blackfoot disease” (BFD) (which has been reported in Taiwanese populations), cardiovascular effects including high blood pressure and circulatory problems. In humans exposed chronically by oral route, skin cancer is the most common type of cancer. In addition, there is the risk of internal tumors (mainly of bladder and lung, and to a lesser extent, liver, kidney, and prostate) (ATSDR, 2007).

2.2.9.1. Renal Effects

Sites of arsenic damage in the kidney include capillaries, tubules and glomeruli, which leaded to hematuria and proteinuria, oliguria, shock and dehydration with a real risk of renal failure, cortical necrosis and cancer (Hopenhayn-rich, Biggs, Smith, Biggs, & Smith, 1998; Zheng et al., 2014).

Mild proteinuria have been noted in rats exposed orally to a single dose of 10 mg As/kg as sodium arsenite, respectively (Flora, Kumar, Kannan, & Rai, 1998).

2.2.9.2. Cardiovascular Effects

There is a limited association between chronic arsenic exposure and peripheral vascular disease, hypertension, and cardiovascular disease. Acute arsenic poisoning may cause both delayed cardiomyopathy, hypotension, shock, transudation of plasma, and vasodilation (Balakumar & Kaur, 2009; Greenberg, Davies, McGowan, Schorer, & Drage, 1979; Ratnaike, 2003; Tchounwou, Centeno, & Patlolla, 2004).

The risk of hypertension and cardiovascular disease mortality due to arsenic ingestion such as an increased of prevalence of peripheral vascular disease among residents with long-term arsenic exposure present in drinking water in Taiwan, Chile, the USA, and Mexico have been associated to inorganic arsenic exposure (Borgono, Vicent, Venturino, & Infante, 1977; Chien Jen Chen et al., 1995; Wang et al., 2007). Gangrene of the extremities, known as "Blackfoot

Disease" (BFD), has also been reported with drinking arsenic-contaminated well water in Taiwan, where the prevalence of the disease increased with increasing age and water arsenic concentration (Chien-jen Chen, Wu, Lee, & Wang, 1988a; C. Tseng, Huang, Huang, & Chung, 2005; W. Tseng, 1977).

2.2.9.3. Neurological Effects

Ingestion of inorganic arsenic can cause injury to the nervous system. Acute and high-dose exposures (1 mg As kg^{-1} per day or more) often lead to encephalopathy, with symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (Bartolomé, Córdoba, Nieto, Fernández-Herrera, & García-Díez, 1999; Cullen, Wolf, & Clair, 1995; Uede & Furukawa, 2003). Intellectual deficits in children have also being associated to exposure to inorganic arsenic (Wasserman et al., 2004).

2.2.9.4. Dermal Effects

Chronic exposures to arsenic can induce a variety of skin insignia of arsenic toxicity (i.e. diffused and spotted melanosis, leucomelanosis, keratosis, hyperkeratosis, dorsum, Bowen's disease, and cancer). Hyperpigmentation may also occur, particularly in body areas where the skin tends to be a little darker (Chakraborti, Rahman, & Paul, 2002; Chowdhury et al., 2000; Maharjan, Watanabe, Ahmad, & Ohtsuka, 2005; G. Mazumder, 2008; Melkonian et al., 2011; NRC, 1999; Smedley & Kinniburgh, 1993).

Several epidemiological studies documented skin disorders in which people consumed drinking water that contained arsenic at the doses of 0.01– 0.1 mg As kg^{-1} per day or more (Ahsan et al., 2000; G. Mazumder, 2008; Milton & Rahman, 1999; Smith, Arroyo, et al., 2000; Tondel et al., 1999).

2.2.9.5. Respiratory Effects

Humans exposed to inorganic arsenic can experience laryngitis, tracheae bronchitis, rhinitis, pharyngitis, shortness of breath, chest sounds (crepitations and/or rhonchi), nasal congestion and perforation of the nasal septum (Gerhardsson et al., 1988; Islam, Nabi, Rahman, & Shamim, 2007; Mazumder et al., 1992; Mazumder et al., 2000; Milton, Asan, Ahman, & Ahman, 2001; Smith, Lingas, & Rahman, 2000).

Increased relative lung weights were seen in rats exposed to 6.66 mg As/kg/day as sodium arsenite 5 days/week for 12 weeks (Schulz, Nagymajtényi, Institoris, Papp, & Siroki, 2002).

2.2.9.6. Pulmonary Effects

The possible role of chronic arsenic ingestion in the genesis of non-malignant pulmonary disease is suggested in a few cases due to exposed to increased concentrations of arsenic.

Chronic cough, restrictive and obstructive lung disease, bronchiectasis and interstitial lung disease are symptoms reported in two studies of arsenic performed in Antofagasta, Chile and in West Bengal, India (Borgono et al., 1977; De, Majumdar, Sen, Guru, & Kundu, 2004).

2.2.9.7. Hematological effects

The hematopoietic system can be affected by both short- and long-term arsenic exposure. Anemia (normochromic normocytic, aplastic and megaloblastic) and leukopenia (granulocytopenia, thrombocytopenia, myeloid, myelodysplasia) are common effects of acute, intermediate and chronic oral exposures. Relatively high doses of arsenic are reported to cause bone marrow depression (Anamika, 2014; Glazener, Francisco, Ellis, Johnson, & Baltimore, 1968; Ratnaike, 2003).

Tice et al. (1997) performed an animal study and found that there was a decrease in polychromatic erythrocytes in the bone marrow of mice treated with 6 mg As/kg/day for 1 or 4 days, however there was no effect at 3 mg As/kg/day.

Similarly, exposure of rats or guinea pigs to 10 or 25 ppm of arsenic as arsenite (approximate doses of 0, 0.92, or 2.3 mg As/kg/day for rats and 0, 0.69, or 1.7 mg As/kg/day for guinea pigs) in the drinking water for 16 weeks (Kannan et al. 2001) resulted in decrease in erythrocyte and leukocyte numbers (rats and guinea pigs), increased blood mean corpuscular volume and corpuscular hemoglobin mass (guinea pigs only), and decreased mean corpuscular hemoglobin concentration (rats only) (Kannan, Tripathi, Dube, Gupta, & Flora, 2001).

2.1.9.8. Gastrointestinal Effects

Gastrointestinal symptoms such as gastrointestinal irritation, including nausea, vomiting, diarrhea, and abdominal pain are common in acute poisoning. Similar signs are also frequently observed in groups or individuals with longer-term, lower-dose exposures (Bartolomé et al., 1999; Cullen et al., 1995; Ratnaike, 2003; Uede & Furukawa, 2003).

More severe symptoms such as hematemesis, hemoperitoneum, gastrointestinal hemorrhage, and necrosis) have been reported in some cases in some people with long-term ingestion (S. Fowler et al., 1975; Morris et al., 1974).

2.2.9.9. Reproductive Effects

Exposure to arsenic in drinking water has been associated with adverse reproductive outcomes such as low birth weight infants, congenital malformations, pregnancy complications, spontaneous abortions, preterm birth and stillbirth in some studies (e.g.: Ahmad et al., 2001; Von Ehrenstein et al., 2006).

2.2.9.10. Hepatic Effects

Studies in humans exposed to inorganic arsenic have noted signs or symptoms of hepatic injury. Clinical examination often reveals that the liver is swollen and tender (Chakraborty & Saha, 1987; Mazumder et al., 1988, 1998; Liu et al., 2002) and analysis of blood sometimes shows elevated levels of hepatic enzymes (Mazumder, 2005; Hernández-Zavala et al., 1998).

Histological examination of the livers of persons chronically exposed has revealed a consistent finding of portal tract fibrosis leading in some cases to portal hypertension and bleeding from esophageal varices (Guha Mazumder, 2005; Guha Mazumder et al., 1988; Morris et al., 1974; Szuler, Williams, Hindmarsh, & Park- Dincsoy, 1979).

Lipid vacuolation and fibrosis were seen in the livers of rats exposed to 12 mg As/kg/day as arsenate in the drinking water for 6 weeks (Fowler, Woods, & Schiller, 1977).

2.2.9.11. Diabetes *Mellitus*

Diabetes *mellitus* has been linked with drinking water arsenic exposure. A study where the relationship between ingested inorganic arsenic and prevalence of diabetes *mellitus* in 891 adults residing in southern Taiwan was accessed, found that residents in the “Blackfoot Disease”–endemic areas had a twofold increase in the prevalence of diabetes *mellitus* when compared to residents in Taipei and the entire Taiwan population (Lai et al., 1994). Other study reported an excess mortality from diabetes among the arsenic exposed population in four townships, relative to local and national rates.(Tsai, Wang, & Ko, 1999).

In Bangladesh It was also showed elevated risks for diabetes in people exposed to arsenic in their drinking water (Rahman, Tondel, Ahmad, & Axelson, 1998; Tondel et al., 1999). However in Utah, was not found significant excess in the number of deaths from diabetes in males and females exposed to elevated levels of arsenic in drinking water (Lewis, Southwick, Ouellet-Hellstrom, Rench, & Calderon, 1999).

2.2.9.10. Carcinogenic Effects

Inorganic arsenic exposure has been shown to modify the expression of a variety of genes related to cell growth and defense as well as to alter the binding of nuclear transcription factors. Arsenate and arsenite enhanced the amplification of a gene that codes for the enzyme dihydrofolate reductase, arsenate being more potent than arsenite. Furthermore, inhibition of DNA repair has been demonstrated in arsenic-treated cells (ATSDR, 2007).

Based on the evidence that arsenic and arsenic compounds cause cancer of the bladder, lung, skin, kidney, liver and prostate, the International Agency for Research on Cancer (IARC) has classified inorganic arsenic as carcinogenic to humans. However, evidence of dose–response relationships that are not attributed to chance or bias have been proven only for lung, bladder and skin cancer (IARC, 1980, 2012).

There is a large number of epidemiological studies and case reports suggesting that the ingestion of inorganic arsenic increases the risk of developing skin cancer (Chen et al., 2003; Freeman, Dennis, Lynch, Thorne, & Just, 2004; Guo, Yu, Hu, & Monson, 2001; Hsueh et al., 1995; Lewis et al., 1999; Lien, Tsai, Lee, & Hsiao, 1999; Lüchtrath, 1983; Mitra et al., 2004; Morris et al., 1974; Sommers & McManus, 1953; W. Tseng, 1977).

In Taiwan, multiple ecological studies based on mortality from skin cancer found consistent gradients of increasing risk with average level of arsenic in drinking water (Chen & Wang, 1990; Chen, Wu, Lee, & Wang, 1988b; Chen, Chuang, Lin, & Wu, 1985; Tsai et al., 1999; Wu, Kuo, Hwang, & Chen, 1989). Other study performed in artesian wells in southwestern Taiwan with 40,421 participants, observed an eight-fold difference in the prevalence of skin cancer lesions from the highest to the lowest category of arsenic concentration (>600 μg/L and and <300 μg/L, respectively) (Tseng et al., 1968).

In a cohort study (654 participants) in southwestern Taiwan it was also observed an incidence rate of 14.7 cases of skin cancer/1000 person–years. They also found that the risks were significantly related to the duration of consumption of artesian well-water, average concentration of arsenic, duration of living in the area endemic for “blackfoot” disease and the cumulative arsenic exposure index (Hsueh et al., 1995).

In Hungary, Romania, and Slovakia a case–control study observed a positive association between Basal Cell Carcinoma (BCC) and exposure to inorganic arsenic through drinking water with concentrations < 100 μg/L(Leonardi et al., 2012).

In addition to the risk of skin cancer, there are several studies that reported that ingestion of arsenic may increase the risks of internal cancers as well (e.g.: Chen, Wu, & Kuo, 1992; Chen, Chuang, You, Lin, & Wu, 1986; Chen, Wu, Lee, & Wang, 1988b; Chen, Chuang, Lin, & Wu, 1985; Chen & Wang, 1990; Chiou et al., 1995; Ferreccio, González Psych, Milosavjlevic Stat, Marshall Gredis, & Sancha, 1998; Hopenhayn-rich et al., 1998; Kurttio, Pukkala, & Kahelin, 1999; Lewis et al., 1999; Rivara, Cebrián, Corey, Hernández, & Romieu, 1997; Wu, Kuo, Hwang, & Chen, 1989).

There is increasingly evidence that long-term exposure to arsenic can result in the development of bladder cancer (Bates et al., 2004; Chen et al., 1992; Chen et al., 2003; Chiou et al., 1995; Guo et al., 2001; Karagas et al., 2004; Steinmaus, Yuan, Bates, & Smith, 2003). Ecological studies in southwestern and northeastern Taiwan have observed an increase in mortality from urinary bladder cancer due to exposure to arsenic via drinking water (Chen & Wang, 1990; Chen et al., 1988b; Chen et al., 1985; Wu et al., 1989).

It was estimated concentrations of arsenic in well water that were associated with a 1% increase in the risk of developing bladder cancer in a Taiwanese population (Morales, Ryan, Kuo, Wu, & Chen, 2000). In Argentina, other study reported an increased risk of bladder cancer in both sexes associated with arsenic exposure (Aballay, Diaz Mdel, Francisca, & Munoz, 2012).

Studies have also suggested that chronic oral exposure to arsenic may result in the development of respiratory tumors and increased incidence of lung cancer (Ferreccio et al., 1998; Guo, 2004; Smith, Goycolea, Haque, & Biggs, 1998).

Cohort studies in southwestern Taiwan observed a positive dose response relationship between the exposure to artesian well water and lung cancer: it was found estimated concentrations of arsenic in well water that were associated with a 1% increase in the risk of developing lung cancer in a Taiwanese population (Morales et al., 2000).

In northern Chile, a study of arsenic-exposed individuals reported significantly increased odds ratio for lung cancer among subjects with ≥30 µg As/L of drinking water although when adjusted for socioeconomic status, smoking, and other factors, the increase was only significant at 60 µg As/L or greater (Ferreccio et al., 1998). Other cohort study in northeastern Taiwan found no apparent increased risk concentrations between 10 and 100 µg/L arsenic, although these associations tended to increase with longer durations of exposure (Chen et al., 2010).

3. Objectives

The overall aim of this project was to evaluate and apply methods to estimate the burden of disease of dietary exposure to chemical hazards, using exposure to inorganic arsenic in Denmark as a case study. The specific objectives were to:

- Estimate the burden of disease of dietary exposure to inorganic arsenic in Denmark in terms of Disability Adjusted Life Years.
- Estimate the relative contribution of different foods for this burden.
- Compare results with burden of disease estimates for other foodborne hazards in Denmark – risk ranking.

4. Materials and Methods

4.1. Burden of Disease Model

To estimate the burden of disease of dietary exposure to inorganic arsenic, a model that incorporates three modules was developed for this study: an Exposure Assessment Module, where the mean daily exposure to inorganic arsenic of the Danish Population was estimated. This estimate was integrated with a Health Outcome Module, in which the probability of occurrence of the selected health outcomes following the exposure to inorganic arsenic was estimated based on dose-response relationships from some published studies. The third component is the DALY Module, where the probability of occurrence of the health outcomes, estimates of life expectancy, disease duration and disability weights was used to calculate the BoD in terms of DALY's (Jakobsen et al., 2016).

Figure 4 represents the model of burden of disease outlined.

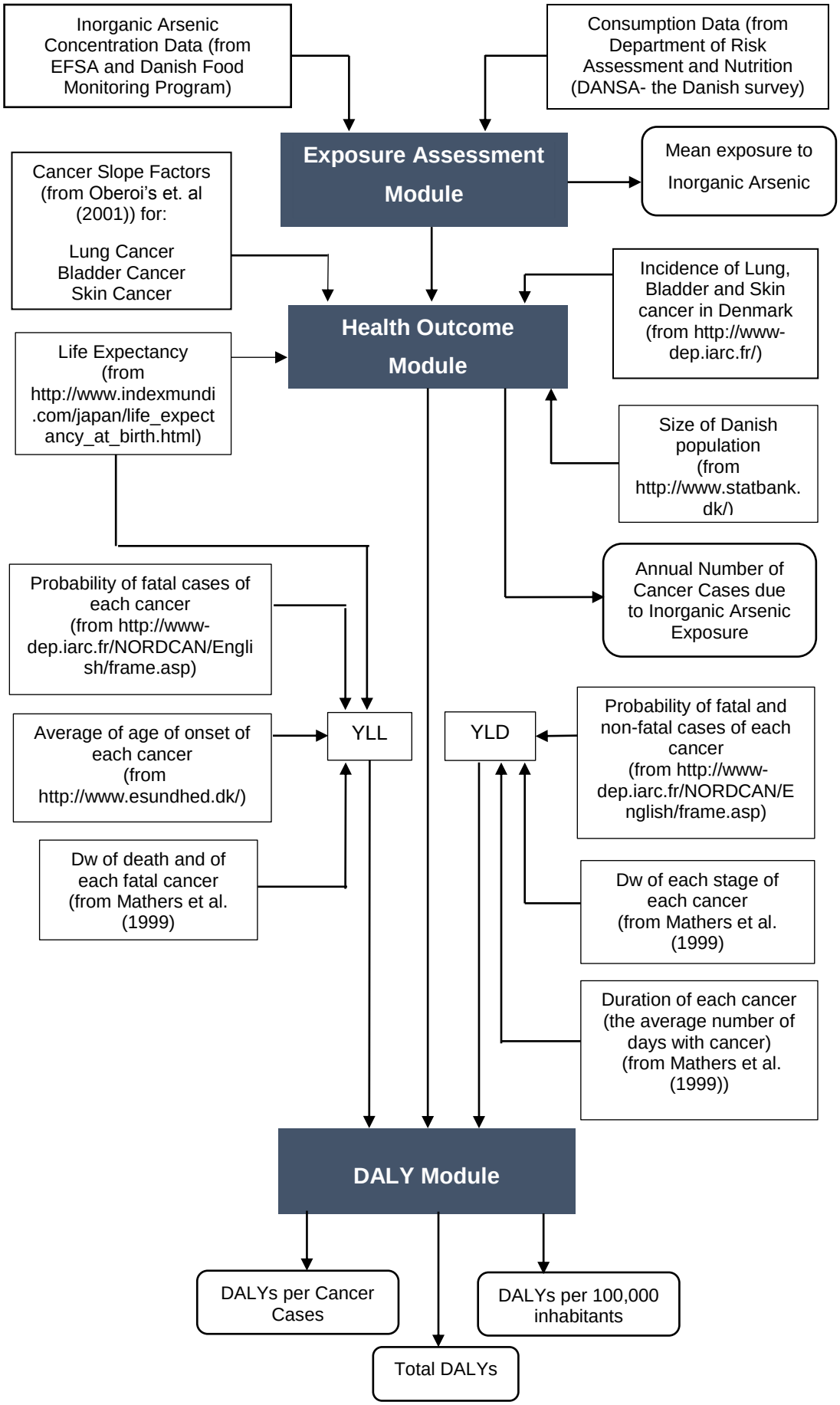

Figure 4 – Outline of the burden of disease of dietary exposure to inorganic arsenic model.

4.1.1. Exposure Assessment Module

Exposure was defined as the mean daily intake over a lifetime of µg iAs per kg bodyweight. Exposure Dietary Intake (EDI) was calculated by:

$$EDI = \sum_{f=1}^{F} \frac{Amount_f \times Conc._{xf}}{Bw \times N}$$

(Eq.1),

where, $Amount_f$ is average portion size for food *f* (g/day), $Conc_f$ is the substance *x* in food *f* (µg/g), *Bw* is the body weight of consumer (kg) and *N* is the number of survey days.

4.1.1.1. Concentration Data

Concentration data for inorganic arsenic from EFSA collected at the EU-level since 2000 to 2014 were compiled. Food samples collected in Denmark were: breakfast cereals; cockle (*Cardium edule*); crispbread rye; crustaceans and maize popped.

Inorganic arsenic concentration data in rice samples was taken from the Danish food monitoring program (Petersen et al., 2011).

4.1.1.2. Consumption Data

Consumption data was obtained from the Danish Dietary Survey of Diet and Physical Activity (DANSA) collected from 2002 to 2014. A total of 3847 consumers between ages 4 and 75 participated in the study. Only consumers with 7 -day recall and with bodyweight information were included in our study, giving a total of 866.

To estimate the mean daily inorganic arsenic intake in the Danish population, the equation 1 was applied to each individual by multiplying the consumption of each food item per the concentration of inorganic arsenic present in food and then the result was divided per the body weight of each individual and per the survey days (seven).

To present the results, all individuals were divided in age groups (4-14 years old; 15-44; 45-64 and more than 65 years) and consumption data was aggregated with concentration data (Table 1) to create food groups.

Table 1- Food groups based on consumption and concentration data aggregation.

Food items	Food Group
Cornflakes	Breakfast Cereals
Oatmeal	
Cornflakes frosted	
Muesli	
Crispbread rye	Crispbread Rye
Crispbread rye coarse (*husmans*)	
Crab claws	Crustaceans
Shrimp frozen	
Shrimp canned	
Clam raw	Cockle
Clam canned	
Popcorn	Maize popped
Brown Rice	
Polished Rice	
Parboiled rice	
Rice cakes	Rice cakes

4.1.2. Health Outcome Module

4.1.2.1. Choice of Health Effects

Arsenic exposure can lead to a wide range of health effects (see 2.1.9). For the burden of disease model, non-cancer health outcomes were discarded because their disability can be regarded as negligible (Max Hansen, Personal Communication).

Lung, bladder and skin cancers were accounted because only for those there is conclusive evidence for dose-response relationships.

4.1.2.2. Dose-Response Model

Cancer slope factors for lung, bladder and lung cancer were taken from Oberoi's et al. (2011). Oberoi's et al. (2011) used data adapted from Morales et al. (2000), where the authors provided a risk assessment based on re-analyses of data originally reported in early studies from arsenic-endemic region of southwestern Taiwan (C Chen et al., 1992; Wu et al., 1989).

For skin cancer, the slope factor was adapted from United States EPA IRIS database (USEPA, 1988).

4.1.2.3. Cancer- Risk Estimation

The cancer-risk from a dietary exposure in a given population, expressed as the annual number of cases (AC), was calculated by multiplying the slope factor for each cancer type (Table 2) with the estimated range of daily dietary inorganic arsenic exposure, the population size and divided by the life expectancy of the same population:

$$AC = \frac{N_{pop} \times y \times SF}{LE_{pop}}$$

(Eq. 2),

where N_{pop} is the size of the exposed population, y is the range of daily dietary inorganic arsenic exposure in µg/kg bw, SF is the slope factor and LE_{pop} is the life expectancy of the exposed population.

Table 2 – Slope factors or cancer potency factors for risk of each arsenic-related cancer from Oberoi's et al. (2011).

Cancer Type	Slope factor (increased population risk per µg iAs/day)	
	Males	Females
Bladder	1.27×10^{-5}	1.98×10^{-5}
Lung	1.37×10^{-5}	1.94×10^{-5}
Skin	1.50×10^{-5}	1.50×10^{-5}

Life expectancy from Japan was used (accessed in http://www.indexmundi.com/japan/life_expectancy_at_birth.html) due to the highest worldwide for men and women, which translates the population best health (Table 3).
The Danish population size (Table 4) was obtained from the national Danish statistical institute (http://www.statbank.dk/).

Table 3 – Life expectancy from Japan for males and females.

Life expectancy	
Male	81,7
Female	88,6

Table 4 –Danish population size of the year 2015 for males and females.

Danish Population Size (2015)	
Male	2600618
Female	2637041

4.1.3. DALY Module

DALY module was estimated by using health statistics and disability weights (Dw) to estimate the average DALY per cancer in Denmark by:

$$DALY_{ave/case} = \left(t_f \times dw_f \times p_f\right) + \left(t_{nf} \times dw_{nf} \times p_{nf}\right) + (YLL \times p_f)$$

(Eq.3),

where t_f is the duration of disease of fatal cancer in years, d_{wf} is the disability weight of fatal cancer, p_f is the probability of a cancer being fatal, t_{nf} is the duration of disease of non-fatal cancer in years, dw_{nf} is the disability weight for non-fatal cancer, p_{nf} is the probability of a cancer being non-fatal and YLL is the life years lost due to premature death to a fatal cancer. YLD_f (fatal cancer) and YLD_{nf} (non-fatal cancer) are given by the first and second terms in equation 3, respectively.

DALY attributed to inorganic arsenic per year per cancer type or total cancer (total DALYs) was calculated by:

$$DALY_{iAs} = AC_{iAs,ep} \times DALY\frac{ave}{case}$$

(Eq.4),

Where $AC_{iAs.ep}$ is the annual cancer cases per endpoint or total cancer due to inorganic arsenic exposure (Eq. 2).

The total burden of disease of inorganic arsenic estimates per 100,000 inhabitants is calculated by multiplying the DALY attributed to inorganic arsenic per year per cancer ($DALY_{iAs}$) per 100,000 inhabitants and divide it per the Danish population size.

The contribution that the food groups have in relation to the total DALYs of the burden of each cancer attributed to foodborne inorganic arsenic intake was estimated. The first step was to calculate the contribution that of each food group has in relation to total exposure by dividing the mean of exposure to inorganic arsenic through each food group per the total mean exposure. Then, this contribution was multiplied per the total DALYs of burden of each cancer type.

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4.1.3.1. Years Lived with Disability (YLD)

The probability of cancer being non-fatal was based on the number of cases of patient that survived with cancer (5 years age-standardized relative survival) (accessed in http://www-dep.iarc.fr/NORDCAN/English/frame.asp) and the probability of a cancer being fatal was calculated by subtracting 1 per the probability of being non-fatal.

The values of disability weights were taken from The Burden of Disease and Injury in Australia (Mathers et al. 1999) because they were more specific for the selected health outcomes.

To attribute values of disability weights for some cancers, the pathological cell types have to be considered. For lung cancer, the most common type associated to inorganic arsenic exposure is squamous cell carcinoma (SqCC), adenocarcinoma and cell carcinoma (H. Guo; Heck et al., 2009). Disability weight for small cell cancer was considered for this type of cancer.

Some studies referred above (2.1.9.10) reported that non-melanoma skin cancer is the histologic type usually associated with inorganic arsenic intake, however other studies found a dose-related increase in the risk of melanoma skin cancer. In this case, values of disability weight for melanoma skin cancer was considered because is the only one that can be fatal compared with non-melanoma skin cancers.

Following the approach of the burden of disease and injury in Australia (Mathers et al. 1999) the cell types for bladder cancer were not specified.

For the values of disability weight for non-fatal cancer, the long term sequelae related to each cancer were selected. For non-fatal lung cancer and non-fatal skin cancer disability weight values for chronic obstructive pulmonary disease and skin diseases (health effects mentioned in 2.1.9.7 and 2.1.9.4) were considered. It was assumed that no long-term sequelae in the bladder would occur after treatment and recovery, so a disability weight of zero was selected for non-fatal bladder cancer.

The time lived with fatal disease for all stages (diagnosis plus primary care, the state after intentionally primary therapy, dissemination, terminal phase and rest of live) was considered to be one year for all stages except the terminal phase that was considered to have a duration of one month (0.083 years). The time lived with non-fatal disease was considered to be one year for the diagnosis plus primary care stage and five years for the state after intentionally primary therapy. After that is assumed that the patients are cured so the dissemination stage and the terminal phase are considered as not existing. This assumptions were adapted from the Australian Burden of Disease and injury Study (Mathers et al. (1999)). Regarding to the rest of life stage, it was only considered for non-fatal cancers and the duration of this stage was obtained by subtracting life expectancy per the age of onset and per the sum of the years lived with cancer.

Disability weights values for calculate YLD_f and YLD_{nf} were estimated by dividing the sum of years lived with disability (fatal and non-fatal) per the sum of the weighted Dw of all stages.

4.1.3.2. Years of Life Lost due to Premature Mortality (YLL)

As described above, YLL is obtained by the sum of the probability of a cancer being fatal with the residual expected individual life span at the age of death and with the disability weight for death.

The residual expected individual life span at the age of death is obtained by subtracting the life expectancy per the average age of onset retired from the Danish national health registers of the year 2014 (accessed in http://www.esundhed.dk/) (Table 5) and per the sum of years lived with disability.

The disability weight for death, as described above is 1.

Table 5- Average age of onset of lung, bladder and skin cancer (males and females).

Cancer type	Gender	Average age of onset
Lung Cancer	Male	70.18
	Female	69.65
Bladder Cancer	Male	70.66
	Female	70.35
Skin Cancer	Male	69.85
	Female	65.24

5. Results

5.1. Exposure Assessment Module

In Table 6 is represented how consumption and concentration datawere grouped with the respective mean of inorganic arsenic concentrations and standard deviations (S.D.).

Table 6- Consumption and concentration data of inorganic arsenic with respective mean concentration (µg/g) and standard deviation (S.D.).

Consumption Data	Concentration data	Mean concentration (µg/g)	S.D.
Cornflakes	Breakfast Cereals	0.069	0.035
Oatmeal			
Cornflakes (frosted)			
Muesli			
Crispbread (rye)	Crispbread (rye)	0.024	0.002
Crispbread (rye, coarse (*Husmans)*)			
Crab claws (canned)	Crustaceans	0.236	N/A
Shrimp (frozen)			
Shrimp (canned)			
Clam (raw)	Cockle (*Cardium edule*)	0.199	N/A
Clam (canned)			
Popcorn	Maize, popped	0.310	N/A
Brown Rice	Brown Rice	0.162	0.938
	Brown Rice (red)		
	Brown Rice (Black)		
	Black Rice		
	Black Rice (parboiled)		
	Black Rice, organic		
	Red Rice, organic		
	Parboiled rice (wild)		
	Wild Rice		
Polished Rice (raw)	White Rice	0.075	0.127
Parboiled Rice (raw)	Parboiled Rice	0.088	0.444
	Jasmin Rice		
	Basmati Rice		
Rice Cakes	Rice cakes	0.311	0.731
	Rice cakes with salt		
	Rice cakes without salt		
	Rice cakes with corn		

N/A – Not applicable

The inorganic arsenic exposure dietary intake estimated through all food items and per age group is present in tables in annex.

The estimated daily exposure to inorganic arsenic through food in the Danish population was estimated to be 0.10 [95% UI: 0.01; 0.33] µg/kg bw/day and 0.08 [95% UI: 0.01; 0.26] µg/kg bw/day (Table 7).

Table 7 – Mean dietary exposure to inorganic arsenic (µg/kg bw/day) in Denmark.

Mean exposure (µg/kg bw/day)	
Males	Females
0.10 [95% UI: 0.01; 0.33]	0.08 [95% UI: 0.01; 0.26]

The estimated dietary exposure to inorganic arsenic through food groups that all individuals (divided per age groups) are exposed is presented in Table 8 and Figure 5 for males and in Table 9 and Figure 6 for females.

Table 8 – Estimated mean dietary exposure to inorganic arsenic (µg/kg bw/day) [95% UI] in males.

Mean exposure (µg/kg bw/day)				
Food Groups	Age groups (years)			
	4-14	15-4	45-64	+65
Breakfast Cereals	0.130 [95% UI: 0.000;0.184]	0.058 [95% UI: 0.000;0.101]	0.045 [95% UI: 0.000;0.078]	0.033 [95% UI: 0.000;0.067]
Crispbread	0.001 [95% UI: 0.000;0.005]	0.000 [95% UI: 0.000;0.002]	0.000 [95% UI: 0.000;0.002]	0.000 [95% UI: 0.000;0.002]
Crustaceans	0.013 [95% UI: 0.000;0.068]	0.012 [95% UI: 0.000;0.041]	0.012 [95% UI: 0.000;0.043]	0.013 [95% UI: 0.000;0.068]
Cockle	0.000 [95% UI: 0.000;0.000]	0.001 [95% UI: 0.000;0.004]	0.001 [95% UI: 0.000;0.003]	0.001 [95% UI: 0.000;0.005]
Maize	0.019 [95% UI: 0.000;0.136]	0.002 [95% UI: 0.000;0.028]	0.001 [95% UI: 0.000;0.007]	0.000 [95% UI: 0.000;0.000]
Rice	0.024 [95% UI: 0.000;0.042]	0.013 [95% UI: 0.000;0.022]	0.008 [95% UI: 0.000;0.015]	0.006 [95% UI: 0.000;0.013]
Rice Cakes	0.017 [95% UI: 0.000;0.139]	0.001 [95% UI: 0.000;0.025	0.001 [95% UI: 0.000;0.006]	0.001 [95% UI: 0.000;0.042]

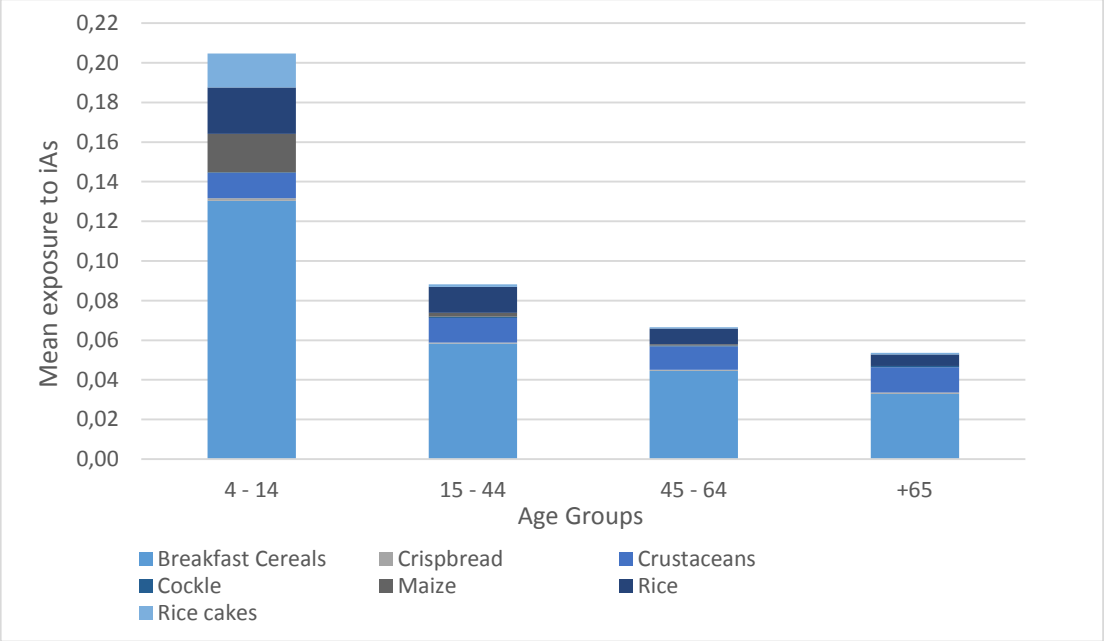

Figure 5- Estimated mean dietary exposure to inorganic arsenic (µg/kg bw/day) [95% UI] for males.

Table 9 - Estimated mean dietary exposure to inorganic arsenic (µg/kg bw/day) [95% UI] in females.

Mean exposure (µg/kg bw/day)				
Food Groups	Age groups (years)			
	4-14	15-44	45-64	+65
Breakfast Cereals	0.088 [95% UI: 0.000;0.135]	0.044 [95% UI: 0.000;0.073]	0.032 [95% UI: 0.000;0.057]	0.026 [95% UI: 0.000;0.046]
Crispbread	0.002 [95% UI: 0.000;0.005]	0.001 [95% UI: 0.000;0.003]	0.001 [95% UI: 0.000;0.002]	0.001 [95% UI: 0.000;0.003]
Crustaceans	0.009 [95% UI: 0.000;0.023]	0.016 [95% UI: 0.000;0.037]	0.017 [95% UI: 0.000;0.048]	0.014 [95% UI: 0.000;0.035]
Cockle	0.000 [95% UI: 0.000;0.000]	0.001 [95% UI: 0.000;0.003]	0.001 [95% UI: 0.000;0.004]	0.000 [95% UI: 0.000;0.003]
Maize	0.014 [95% UI: 0.000;0.112]	0.003 [95% UI: 0.000;0.046]	0.001 [95% UI: 0.000;0.016]	0.001 [95% UI: 0.000;0.000]
Rice	0.021 [95% UI: 0.000;0.034]	0.010 [95% UI: 0.000;0.023]	0.007 [95% UI: 0.000;0.013]	0.004 [95% UI: 0.000;0.011]
Rice Cakes	0.024 [95% UI: 0.000;0.152]	0.003 [95% UI: 0.000;0.029]	0.002 [95% UI: 0.000;0.025]	0.001 [95% UI: 0.000;0.020]

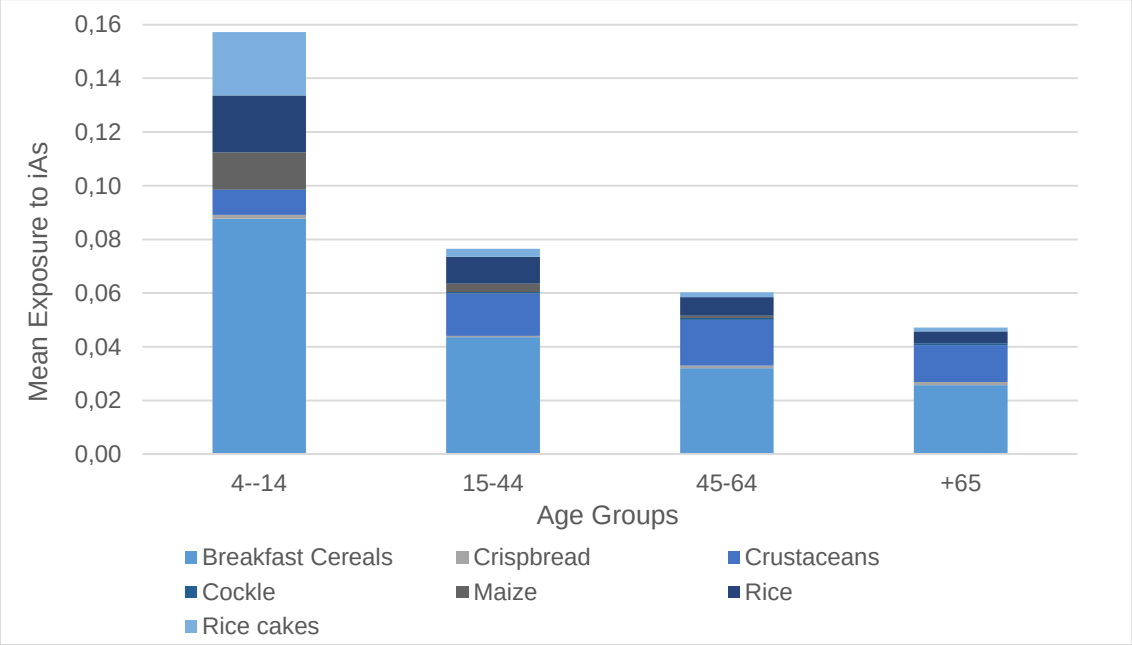

Figure 6 - Estimated mean dietary exposure to inorganic arsenic (µg/kg bw/day) [95% UI] for females.

5.2. Health Outcome Module

The estimated annual number of lung, bladder and skin cancer cases attributed to inorganic arsenic exposure through foods is presented in Table 10. It was estimated a number of 0.087, 0.089 and 0.082 cases of lung, bladder and skin cancer respectively, each year due to foodborne exposure to inorganic arsenic in Denmark and a total number of 0.26 annual cancer cases.

Table 10 - Annual number of lung, bladder and skin cancer cases due to inorganic arsenic dietary exposure in Denmark.

Annual Number of Cases (AC_{iAs})						
	Lung Cancer		Bladder Cancer		Skin Cancer	
	Male	Female	Male	Female	Male	Female
	0.04	0.047	0.043	0.046	0.047	0.035
Total	**0.087**		**0.089**		**0.082**	
	0.26					

5.3. DALY Module

The probability of lung, bladder and skin cancer being fatal and non-fatal is shown in Table 11.

Table 11 – Probability of fatal and non-fatal cases of lung, bladder and skin cancer.

Cancer Type	Parameter	Value	Min	Max
Lung Cancer (male)	P (non-fatal)	0.12	0.12	0.13
	P (fatal)	0.88	0.88	0.87
Lung Cancer (female)	P (non-fatal)	0.17	0.17	0.18
	P (fatal)	0.83	0.83	0.82
Bladder Cancer (male)	P (non-fatal)	0.74	0.72	0.75
	P (fatal)	0.26	0.28	0.25
Bladder Cancer (female)	P (non-fatal)	0.65	0.63	0.67
	P (fatal)	0.35	0.37	0.33
Skin Cancer (male)	P (non-fatal)	0.90	0.89	0.91
	P (fatal)	0.10	0.11	0.09
Skin Cancer (female)	P (non-fatal)	0.95	0.94	0.96
	P (fatal)	0.05	0.06	0.04

The time lived with fatal disease for all stages (diagnosis plus primary care, state after intentionally primary therapy, dissemination, terminal phase and rest of live), the values of Dw and weighted Dw for both fatal and non-fatal disease are present in the Tables 12, 13 and 14.

Table 12 – Duration per stage, Dw and weighted Dw of fatal and non-fatal lung cancer (males and females) for all stages.

Duration per stage (years)	Diagnosis + primary care	State after intentionally primary therapy	Dissemination	Terminal phase	Rest of life
Male					
Duration fatal cancer	1	1	1	0.08	0
Dw fatal	0.68	0.47	0.91	0.93	0
Weighted Dw	0.68	0.47	0.91	0.0775	0
Duration non-fatal cancer	1	5	0	0	5.53
DW non-fatal	0.68	0.47	0	0	0.53
Weighted Dw	0.68	2.35	0	0	2.93
Female					
Duration fatal cancer	1	1	1	0.08	0
Dw fatal	0.68	0.47	0.91	0.93	0
Weighted Dw	0.68	0.47	0.91	0.08	0
Duration non-fatal cancer	1	5	0	0	12.95
DW non-fatal	0.68	0.47	0	0	0.53
Weighted Dw	0.68	2.35	0	0	6.86

Table 13- Duration per stage, Dw and weighted Dw of fatal and non-fatal bladder cancer (males and females) for all stages.

Duration per stage (years)	Diagnosis + primary care	State after intentionally primary therapy	Dissemination	Terminal phase	Rest of life
Male					
Duration fatal cancer	1	1	1	0.08	0
Dw fatal	0.27	0.18	0.64	0.93	0
Weighted Dw	0.27	0.18	0.64	0.08	0
Duration non-fatal cancer	1	5	0	0	0
DW non-fatal	0.27	0.18	0	0	0
Weighted Dw	0.27	0.9	0	0	0
Female					
Duration fatal cancer	1	1	1	0.08	0
Dw fatal	0.27	0.18	0.64	0.93	0
Weighted Dw	0.27	0.18	0.64	0.08	0
Duration non-fatal cancer	1	5	0	0	0
DW non-fatal	0.27	0.18	0	0	0
Weighted Dw	0.27	0.9	0	0	0

Table 14- Duration per stage, Dw and weighted Dw of fatal and non-fatal skin cancer (males and females) for all stages.

Duration per stage (years)	**Diagnosis + primary care**	**State after intentionally primary therapy**	**Dissemination**	**Terminal phase**	**Rest of life**
Male					
Duration fatal cancer	1	1	1	0.08	0
Dw fatal	0.19	0.19	0.81	0.93	0
Weighted Dw	0.19	0.19	0.81	0.08	0
Duration non-fatal cancer	1	5	0	0	5.85
DW non-fatal	0.07	0.19	0	0	0.06
Weighted Dw	0.07	0.95	0	0	0.33
Female					
Duration fatal cancer	1	1	1	0.08	0
Dw fatal	0.19	0.19	0.81	0.93	0
Weighted Dw	0.19	0.19	0.81	0.08	0
Duration non-fatal cancer	1	5	0	0	17.36
DW non-fatal	0.07	0.19	0	0	0.06
Weighted Dw	0.07	0.95	0	0	0.97

In Tables 15, 16 and 17 is represented the results of YLD, YLL and $DALY_{per\ case}$ for lung, bladder and skin cancer respectively, with the parameters used. It was estimated a total number of 26.67 DALYs per lung cancer, 9.72 DALYs per bladder cancer and 5.19 DALYs per skin cancer (Figure 7).

Table 15- YLD, YLL and $DALY_{per\ case}$ estimates for lung cancer with respective parameters used.

Lung Cancer					
	Health outcome	Duration (years)	DW	Proportion of cases	SUM
Male					
YLD	Morbidity: fatal cancer	3.08	0.69	0.88	1.88
	Morbidity: non-fatal cancer	11.53	0.52	0.12	0.72
YLL	Mortality: fatal cancer	8.45	1	0.88	7.44
$DALY_{per\ case}$					**10.03**
Female					
YLD	Morbidity: fatal cancer	3.08	0.69	0.83	1.77
	Morbidity: non-fatal cancer	18.95	0.523	0.17	1.70
YLL	Mortality: fatal cancer	15.86	1	0.83	13.17
$DALY_{per\ case}$					**16.64**

Table 16- YLD, YLL and $DALY_{per\ case}$ estimates for bladder cancer with respective parameters used.

Bladder Cancer					
	Health outcome	Duration (years)	DW	Proportion of cases	SUM
Male					
YLD	Morbidity: fatal cancer	3.08	0.38	0.26	0.30
	Morbidity: non-fatal cancer	6	0.20	0.74	0.87
YLL	Mortality: fatal cancer	7.96	1	0.26	2.07
$DALY_{per\ case}$					**3.24**
Female					
YLD	Morbidity: fatal cancer	3.08	0.38	0.35	0.41
	Morbidity: non-fatal cancer	6	0.20	0.65	0.76
YLL	Mortality: fatal cancer	15.17	1	0.35	5.31
$DALY_{per\ case}$					**6.48**

Table 17- YLD, YLL and $DALY_{per\ case}$ estimates for skin cancer with respective parameters used.

Skin Cancer					
	Health outcome	Duration (years)	DW	Proportion of cases	SUM
Male					
YLD	Morbidity: fatal cancer	3.08	0.41	0.1	0.13
	Morbidity: non-fatal cancer	11.85	0.11	0.9	1.21
YLL	Mortality: fatal cancer	8.77	1	0.1	0.88
$DALY_{per\ case}$					**2.22**
Female					
YLD	Morbidity: fatal cancer	3.08	0.41	0.05	0.06
	Morbidity: non-fatal cancer	23.36	0.09	0.95	1.89
YLL	Mortality: fatal cancer	20.28	1	0.05	1.01
$DALY_{per\ case}$					**2.97**

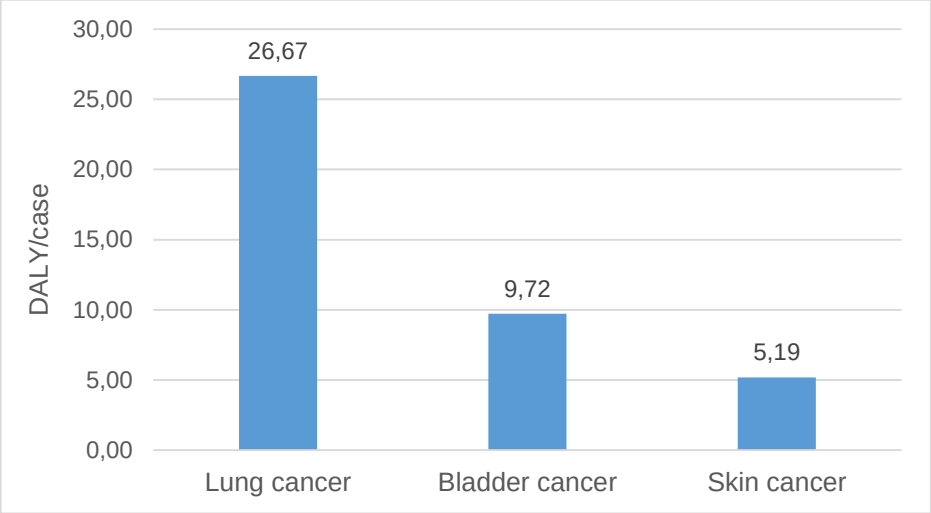

Figure 7- DALY/case caused by inorganic arsenic induced lung, bladder and skin cancer in Denmark.

The results of the total burden of disease attributed to inorganic arsenic are present in Table 18. A health loss of 0.035 DALY per 100,000 inhabitants and a burden of total cancer of 1.83 DALYs attributed to dietary inorganic arsenic were estimated.

Table 18 – Total DALYs attributed to inorganic arsenic per lung, bladder and skin cancer and total burden of disease estimates per 100,000 inhabitants in Denmark.

Cancer type		Total DALY	DALY/100,000
Lung cancer	Male	0.402	0.015
	Female	0.778	0.029
Bladder cancer	Male	0.140	0.005
	Female	0.297	0.011
Skin cancer	Male	0.105	0.004
	Female	0.105	0.004
Total		**1.83**	**0.035**

The results of the contribution that the food groups have in relation to the total DALYs of the burden of each cancer type attributed to foodborne inorganic arsenic intake are present in Tables 19 and 20.

It was estimated that the group “Breakfast Cereals contributed with 61% of the total exposure of inorganic arsenic for males and 55% for females, the group “Cockle” and “Crispbread” contributed with 1% for both genders, “Crustaceans” contributed with 15% for males and 19% for females, “Maize popped” contributed 5% in males and 4% in females, the contribution of “Rice” was 12% for both genders and “Rice Cakes” contributed with 6% and 7% in males and females respectively.

Table 19 – Relative contribution of food items to total inorganic arsenic exposure and to total DALY for males.

Food Group	Mean exposure	Contribution to total exposure	DALY attributed			%DALY of total
			Lung Cancer	Bladder Cancer	Skin Cancer	
Breakfast cereals	0.054	0.606	0.243	0.085	0.064	61%
Cockle	0.001	0.006	0.002	0.001	0.001	1%
Crispbread rye	0.001	0.010	0.004	0.001	0.001	1%
Crustaceans	0.014	0.151	0.061	0.021	0.016	15%
Maize popped	0.004	0.047	0.019	0.007	0.005	5%
Rice	0.011	0.124	0.050	0.017	0.013	12%
Rice Cakes	0.005	0.056	0.023	0.008	0.006	6%
SUM	0.090	1.000	0.402	0.140	0.105	100%

Table 20 - Relative contribution of food items to total inorganic arsenic exposure and to total DALY for females.

Food Group	Mean exposure	Contribution to total exposure	DALY attributed			%DALY of total
			Lung Cancer	Bladder Cancer	Skin Cancer	
Breakfast cereals	0.044	0.551	0.429	0.1635	0.058	55%
Cockle	0.001	0.007	0.005	0.0020	0.001	1%
Crispbread rye	0.001	0.015	0.011	0.0044	0.002	1%
Crustaceans	0.015	0.186	0.145	0.0553	0.020	19%
Maize popped	0.004	0.045	0.035	0.0133	0.005	4%
Rice	0.010	0.124	0.096	0.0367	0.013	12%
Rice Cakes	0.006	0.073	0.057	0.0216	0.008	7%
SUM	0.080	1.000	0.778	0.2968	0.105	100%

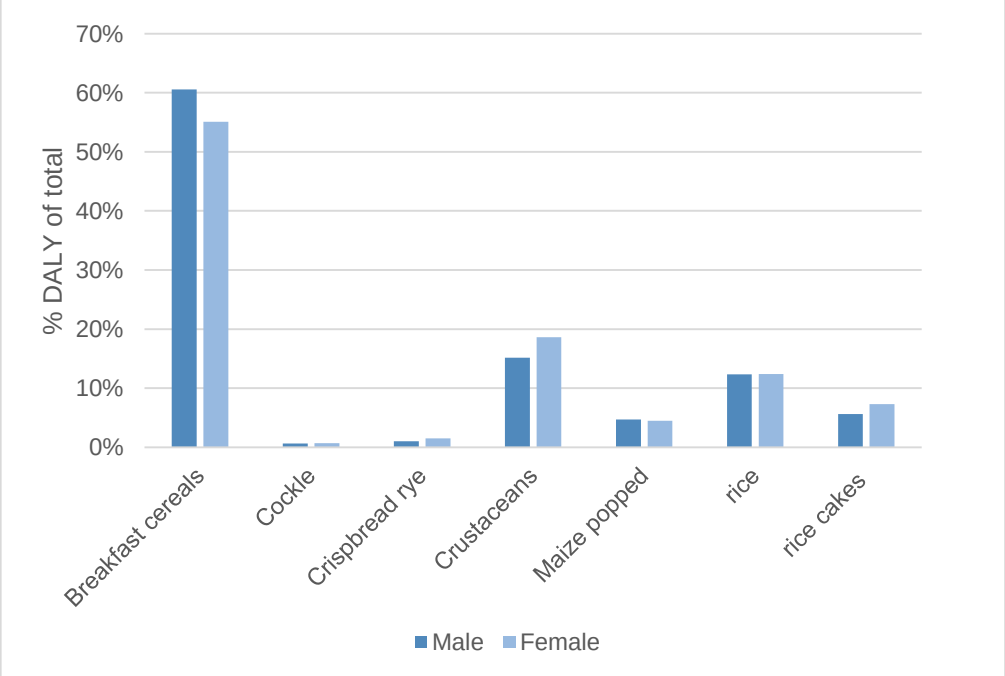

Figure 8 –Contribution of food groups to total DALY

6. Discussion

This study estimated the burden of disease of dietary exposure to inorganic arsenic in Denmark in terms of Disability Adjusted Life Years.

For this estimates, inorganic arsenic was not accounted in water/beverages due to the fact that in Europe, arsenic is found at low levels in water so most of the exposure comes through food that are come from countries where water contamination is higher (accessed in: http://www.nhs.uk/news/2017/05May/Pages/Concerns-about-alleged-harmful-arsenic-levels-in-baby-rice-cakes.aspx).

Regarding to the inorganic arsenic concentration present in all food items it was verified that the concentration range between 0.024 µg/g and 0.311 µg/g.

According to EFSA (2009) rice and rice based-food are considered the foods that have higher levels of inorganic arsenic than other foods because is the only major crop that is grown under flooded conditions and is this flooding that releases inorganic arsenic, normally locked up in soil minerals, which makes it available for the plant to uptake. Concentrations between 0.1-0.4 µg/g was reported by Sun et al. (2008). Jorhem et al. (2008) also reported concentrations of inorganic arsenic in brown rice, parboiled white rice and white rice averaged 0.110 µg/g. In this study the concentrations of inorganic arsenic in brown, polished (white) and parboiled rice were 0.162 µg/g, 0.075 µg/g and 0.088 µg/g, respectively, which does not differ from the concentrations reported by this authors. However rice was not the food with the highest concentrations of inorganic arsenic in this study, but yes the rice cakes with concentrations of 0.311 µg/g.

The second item of food with highest concentrations was maize popped (0.310 µg/g) followed by the crustaceans and cockle (0.236 and 0.199 µg/g respectively). As mentioned above seafood usually has high concentrations of total arsenic but lower levels of inorganic arsenic. Sloth et al. (2008; 2005) reported concentrations of inorganic arsenic in crustaceans from 0.001 and 4.5 mg/kg.

Breakfast cereals and crispbread rye were the food with the lower concentrations (0.069 and 0.024 µg/g respectively).

A mean exposure of 0.10 [95%UI: 0.01; 0.33] (µg/kg bw/day) and 0.08 [95% UI: 0.01; 0.26] (µg/kg bw/day) for males and females respectively was observed (table12). The estimated daily dietary intake of inorganic arsenic for various age group did not differed between them, both for males and females (table 13 and 14). However it was observed that infants of both genders (4-14 years old) have the highest mean exposure to inorganic arsenic (0.21 and 0.16 µg/kg bw/day) mainly contributed per breakfast cereals and rice-cakes.

In the United States and Canada, Yost et al. (1998) reported that the estimated daily dietary intake of inorganic arsenic for various age groups ranged from 8.3 to 14 µg/kg bw/day and from 4.8 to 12.7 µg/kg bw/day for infants and for 60-65 years-old man, respectively. Jorhem et al. (2008) estimated a dietary exposure to inorganic arsenic of 2 µg/kg bw per day from

rice for typical adult European and Tao et al. (1998) reported an average daily exposure of inorganic arsenic from 1.3 in infants to 12.5 µg/kg bw/day in 60-65-year-old men.

Comparing the results of the mean exposure to inorganic arsenic of the Danish population estimated in this study, it can be considered that is relatively lower that the mean exposure calculated by the authors referred above.

In general, the mean exposure was predominantly contributed by breakfast cereals (55-61%), followed by crustaceans (15-19%) and rice (12%) (Tables 20 and 21). Other studies achieved different results and reported the grain-based processed products (non-rice based), in particular wheat bread and the rice the majors contributors to dietary exposure to inorganic arsenic (EFSA, 2014). The National Food Agency in Sweden also identified rice as the major food contributor to the exposure to inorganic arsenic in adults and children (Kollander & Sundstr, 2015).

The average DALY per lung cancer cases in Denmark was the highest, which was estimated as being 26.67 DALYs, per bladder and skin cancer cases, it was calculated 9.72 DALYs and 5.19 DALYs respectively (figure 7).

The number of years lost due to people living with lung cancer is higher (2.6 years for males and 3.5 years for females) compared with bladder and skin cancer: 1.2 years (both genders), 1.3 years (males) and 2 years (females), respectively. The number of years of life lost due to premature mortality due to lung cancer is also higher for lung cancer (7.4 years for males and 13.2 years for females) compared with bladder (2.1 years for males and 5.3 years for females) and with skin cancer (approximately one year for both genders). For this estimates several assumptions were taken into account (from Mathers et al. (1999) study) like the duration of all stages of fatal and non-fatal cancer that were assumed to be equal for all cancers, the cell types of each cancer that were considered for the values of disability weight. Maybe an information more specific information of each type of cancer (e.g. oncologists) could improve this estimates.

To estimate the cancer risk, cancer slope factors for lung, bladder and skin cancer were obtained from Oberoi et al. (2011) study and according to them, the assumption of linear dose-response relationships of arsenic-related cancers is controversial, particularly regarding the mode of carcinogenicity of skin cancer because there are no studies that present the effects of low dose arsenic exposures on skin cancer, which reduces certainty regarding the shape of the lower end of the dose-response curve. So, it is conservative to default to the linear model for determining the skin cancer potency factor. This is one of the reasons that the results should be interpreted carefully.

The annual number of lung, bladder and skin cancer cases attributable to foodborne exposure to inorganic arsenic was estimated to be 0.087, 0.089 and 0.082 respectively resulting in a total of less than 1 case each year (0.26 cancer cases), as is overall burden of disease in terms of DALYs.

Oberoi et al (2011) estimated approximately 150.000 cancer cases due to inorganic arsenic globally. Taking into account that the world population is approximately 7.5 billion inhabitants, the estimated incidence of disease per 100,000 inhabitants (of approximately 2 cancer cases) is substantially higher than the estimates for Denmark presented in this study. Potential explanations for these differences are the use of data from different countries, the variability in the concentrations of arsenic present in food and different consumption patterns of different foods when compared to Denmark.

The number of cancer cases attributable to arsenic estimated in the present study is also lower when compared with the burden of disease of foodborne acrylamide exposure in Denmark estimated by Jakobsen et al. (2016), which reported 5 cancer cases each year.

The average DALY per cancer cases in Denmark was estimated to be 26.67 DALYs for lung cancer, 9.72 DALYs for bladder cancer and 5.19 DALYs for skin cancer, resulting in a total of 41.6 DALYs associated to inorganic arsenic exposure. This result is slightly similar to total DALYs estimated in the acrylamide study (42 total DALYs).

A total burden of 0.04 DALY/100,000 inhabitants was estimated, which is lower or in the same range as estimates of the global and regional burden of disease caused by other chemicals in foods derived by other studies. The WHO's estimates for the European region showed a burden of 0.5 DALY/100,000 for aflatoxin causing liver cancer, 1 DALY/100,000 for dioxins causing hypothyroid and decreased sperm count (Gibb et al., 2015). Jakobsen et al. (2016) estimated a burden of 0.03 DALY/100,000 inhabitants due to dietary acrylamide intake causing endometrial, breast and kidney cancer.

During this study, there were some potential factors that could influence the probability of disease given to inorganic arsenic exposure, that were not taken into account. As an example, the bioavailability of arsenic in different foods varies with the food group or method of processing (e.g.: the probability of rice cooked to contain levels of inorganic arsenic is higher than rice uncooked due to the water used to cook the rice may contain high levels of inorganic arsenic); the complexity of influence of other food constituents in arsenic toxicity and adverse health effects and other carcinogenic hazards and risk factors were not accounted for (e.g.: the validation of the estimated extra cancer cases is very difficult due to the chronicity and multi-causality and also due to the exposure that can take place a long time before the onset of disease).

Burden of disease studies for other foodborne hazards in Denmark have been estimated such as for *Norovirus*, *Campylobacter*, *Salmonella*, *Verocytotoxin-producing Escherichia Coli* (*VTEC)*. The burden of disease estimates an annual number of 51821, 12159 and 5920 cases of diseases associated to *Campylobacter*, *Salmonella* and *VTEC* infections, respectively. A total of 1594 DALYs were estimated for *Campylobacter*, 674 DALYs for *Norovirus*, 389 DALYs for *Salmonella* and 113 DALYs for *VTEC*. (Pires, 2014).

The results obtained in this burden of disease of foodborne inorganic arsenic exposure study are significantly lower when compared with the results of the burden of disease of pathogens referred above. One of the main reason of this difference could be because chemicals can cause very severe diseases (such as cancer), while foodborne pathogens mostly cause middle to moderate gastroenteritis.

The potential reason for the low estimated burden of disease of chemical hazards is, as already mentioned, that it is difficult to establish links between the chemicals and their health outcomes due to their relationships may not observed for years following exposure. Exposure assessment need to account for long-term exposure through food and data linking dose exposure to effect (e.g.: dose- response) are often lacking.

As written previously, burden of disease studies may provide a valuable insight into the scope for further health gains on the global and country level. However, there is some challenges in implementing this types of studies: BoD studies are data-intensive and sharing data is a current problem that should be addressed because it can help defining the nature and magnitude of food safety problems, documenting outbreaks and other public health anomalies and contributing to assessing risk and prioritizing food safety problems, for example by identifying which foods cause these problem, the options for interventions and measure the effect of each intervention; Gender and age specific health and population data is difficult to obtain under some circumstances and age categorization may need to be standardized across different types of data in a country.

Because of the methodological variation between studies it is difficult to assess whether differences in DALY estimates between the studies are due to actual differences in population health or whether these are the results of methodological choices. Overcoming this methodological rigor between burden of disease studies using DALY approach is a critical priority for advancing burden of disease studies. Harmonization of the methodology used and high-quality data can enlarge the detection of true variation in DALY outcomes between populations or over time.

This disease burden of inorganic arsenic exposure through food provides a basis for comparison with disease burden of other food chemicals. Besides that, results show that all methodological choices and assumptions of a burden of disease model need to be careful considered when DALYs are interpreted.

7. Conclusion

Burden of disease studies are an important contribution to determine priorities for public health interventions and, to prioritize ad allocate resources for foodborne disease prevention, to monitor and evaluate the effectiveness of measures taken and to quantify the burden in monetary terms, mainly when there are no consistent global information assembled to describe the full spectrum of foodborne diseases have been conducted in recent years, but the majority have focused mostly on foodborne microbiological pathogens (including bacteria, virus and parasites) and a gap of knowledge on the true impact of foodborne chemical hazards has been recognized.

The Oberoi et al. (2011) study is the only one that estimated the burden of disease caused by arsenic until the present, however they accounted with arsenic present in drinking water and it was at global level. At national and European level, this was the first study that estimates the burden of disease attributed to dietary exposure to inorganic arsenic.

This study estimated that the exposure to inorganic arsenic through food causes a disease burden of 0.04 DALY/100,000 per year in Denmark, which corresponds to 0.26 annual cases of cancer in the population.

The assessment of the burden of disease from chemicals in food is a challenge on several levels due mainly of the health effects caused by chemicals may not be observed for years following exposure.

Models to estimate the burden of chemicals transmitted through foods would be greatly improved by toxicological data on human health after exposure to these chemicals. Despite uncertainties of this model, this study can provide a comparison with other estimations of other chemical hazards, in Denmark and in other countries with representative food-exposure data.

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ANNEX

Table 1 - Estimated mean exposure to iAs (µg/kg bw/day) through Cornflakes

Age Groups	Both sexes	Male	Female
4-14	0.021 [95% UI: 0.000;0.091]	0.025 [95% UI: 0.000;0.095]	0.017 [95% UI: 0.000;0.069]
15-44	0.007 [95% UI: 0.000;0.039]	0.006 [95% UI: 0.000;0.036]	0.008 [95% UI: 0.000;0.051]
45-64	0.005 [95% UI: 0.000;0.027]	0.002 [95% UI: 0.000;0.027]	0.003 95% UI: [0.000;0.025]
+65	0.003 [95% UI: 0.000;0.027]	0.002 [95% UI: 0.000;0.025]	0.003 [95% UI: 0.000;0.026]

Table 2 - Estimated mean exposure to iAs (µg/kg bw/day) through Crispbread rye

Age Groups	Both sexes	Male	Female
4-14	0.001 [95% UI: 0.000;0,005]	0.001 [95% UI: 0.000;0.0050]	0.001 [95% UI: 0.000;0.054]
15-44	0.001 [95% UI: 0.000;0.003]	0.000 [95% UI: 0.000;0.002]	0.001 [95% UI: 0.000;0.050]
45-64	0.000 [95% UI: 0.000;0.002]	0.000 [95% UI: 0.000;0.002]	0.001 [95% UI: 0.000;0.049]
+65	0.001 [95% UI: 0.000;0.003]	0.000 [95% UI: 0.000;0.002]	0.001 [95% UI: 0.000;0.033]

Table 3 - Estimated mean exposure to iAs (µg/kg bw/day) through Crab claws canned

Age Groups	Both sexes	Male	Female
4-14	0.000 [95% UI: 0.000;0.0012]	0.000 [95% UI: 0.000;0.002]	0.000 [95% UI: 0.000;0.000]
15-44	0.001 [95% UI: 0.000;0.006]	0.001 [95% UI: 0.000;0.007]	0.000 [95% UI: 0.000;0.004]
45-64	0.001 [95% UI: 0.000;0.006]	0.000 [95% UI: 0.000;0.005]	0.001 [95% UI: 0.000;0.007]
+65	0.001 [95% UI: 0.000;0.007]	0.001 [95% UI: 0.000;0.0109	0.001 [95% UI: 0.000;0.006]

Table 4 - Estimated mean exposure to iAs (µg/kg bw/day) through Clam raw

Age Groups	Both sexes	Male	Female
4-14	0.000 [95% UI: 0.000;0,0000]	0.000 [95% UI: 0.000;0.0000]	0.00 [95% UI: 0.000;0.000]
15-44	0.000 [95% UI: 0.000;0.006]	0.000 [095% UI:0.000;0.005]	0.000 [95% UI: 0.000;0.006]
45-64	0.000 [95% UI: 0.000;0.003]	0.000 [95% UI: 0.000;0.004]	0.000 [95% UI: 0.000;0.000]
+65	0.000 [95% UI: 0.000;0.000]	0.000 [95% UI: 0.000;0.002]	0.000 [95% UI: 0.000;0.000]

Table 5 - Estimated mean exposure to iAs (µg/kg bw/day) through Clam canned

Age Groups	Both sexes	Male	Female
4-14	0.000 [95% UI: 0.000;0,001]	0.000 [95% UI: 0.000;0.001]	0.000 [95% UI: 0.000;0.000]
15-44	0.000 [95% UI: 0.000;0.003]	0.000 [95% UI: 0.000;0.004]	0.000 [95% UI: 0.000;0.002]
45-64	0.000 [95% UI: 0.000;0.004]	0.000 [95% UI: 0.000;0.003]	0.001 [95% UI: 0.000;0.004]
+65	0.001 [95% UI: 0.000;0.004]	0.001 [95% UI: 0.000;0.006]	0.001 [95% UI: 0.000;0.0037]

Table 6 - Estimated mean exposure to iAs (µg/kg bw/day) through Shrimp frozen

Age Groups	Both sexes	Male	Female
4-14	0.004 [95% UI: 0.000;0.041]	0.005 [95% UI: 0.000;0.057]	0.003 [95% UI: 0.000;0.023]
15-44	0.008 [95% UI: 0.000;0.041]	0.007 [95% UI: 0.000;0.018]	0.008 [95% UI: 0.000;0.039]
45-64	0.008 [95% UI: 0.000;0.051]	0.007 [95% UI: 0.000;0.040]	0.010 [95% UI: 0.000;0.055]
+65	0.008 [95% UI: 0.000;0.061]	0.008 [95% UI: 0.000;0.070]	0.008 [95% UI: 0.000;0.040]

Table 7 - Estimated mean exposure to iAs (µg/kg bw/day) through Shrimp Canned

Age Groups	Both sexes	Male	Female
4-14	0.007 [95% UI: 0.000;0.068]	0.007 [95% UI: 0.000;0.072]	0.006 [95% UI: 0.000;0.054]
15-44	0.006 [95% UI: 0.000;0.042]	0.005 [95% UI: 0.000;0.028]	0.007 [95% UI: 0.000;0.050]
45-64	0.006 [95% UI: 0.000;0.050]	0.005 [95% UI: 0.000;0.051]	0.007 [95% UI: 0.000;0.049]
+65	0.004 [95% UI: 0.000;0.030]	0.004 [95% UI: 0.000;0.028]	0.005 [95% UI: 0.000;0.033]

Table 8 - Estimated mean exposure to iAs (µg/kg bw/day) through Brown Rice

Age Groups	Both sexes	Male	Female
4-14	0.003 [95% UI: 0.000;0.033]	0.004 [95% UI: 0.000;0.047]	0.003 [95% UI: 0.000;0.024]
15-44	0.002 [95% UI: 0.000;0.024]	0.003 [95% UI: 0.000;0.022]	0.002 [95% UI: 0.000;0.024]
45-64	0.002 [95% UI: 0.000;0.013]	0.001 [95% UI: 0.000;0.013]	0.001 [95% UI: 0.000;0.011]
+65	0.000 [95% UI: 0.000;0.007]	0.000 [95% UI: 0.000;0.005]	0.001 [95% UI: 0.000;0.007]

Table 9 - Estimated mean exposure to iAs (µg/kg bw/day) through Parboiled Rice raw

Age Groups	Both sexes	Male	Female
4-14	0.009 [95% UC: 0.000;0.047]	0.009 [95% UI: 0.000;0.045]	0.010 [95% UI: 0.000;0.045]
15-44	0.004 [95% UI: 0.000;0.019]	0.004 [95% UI: 0.000;0.018]	0.004 [95% UI: 0.000;0.018]
45-64	0.003 [95% UI: 0.000;0.014]	0.003 [95% UI: 0.000;0.013]	0.002 [95% UI: 0.000;0.014]
+65	0.002 [95% UI: 0.000;0.011]	0.002 [95% UI: 0.000;0.013]	0.001 [95% UI: 0.000;0.010]

Table 10 - Estimated mean exposure to iAs (µg/kg bw/day) through Polished Rice raw

Age Groups	Both sexes	Male	Female
4-14	0.009 [95% UI: 0.000;0.037]	0.010 [95% UI: 0.000;0.040]	0.009 [95% UI: 0.000;0.030]
15-44	0.005 [95% UI: 0.000;0.023]	0.006 [95% UI: 0.000;0.024]	0.005 [95% UI: 0.000;0.020]
45-64	0.004 [95% UI: 0.000;0.014]	0.004 [95% UI: 0.000;0.017]	0.003 [95% UI: 0.000;0.013]
+65	0.003 [95% UI: 0.000;0.000]	0.003 [95% UI: 0.000;0.014]	0.003 [95% UI: 0.000;0.015]

Table 11 - Estimated mean exposure to iAs (µg/kg bw/day) through Popcorn

Age Groups	Both sexes	Male	Female
4-14	0.017 [95% UI: 0.000;0.130]	0.019 [95% UI: 0.000;0.136]	0.014 [95% UI: 0.000;0.113]
15-44	0.003 [95% UI: 0.000;0.0326]	0.002 [95% UI: 0.000;0.028]	0.003 [95% UI: 0.000;0.046]
45-64	0.002 [95% UI: 0.000;0.0137]	0.001 [95% UI: 0.000;0.007]	0.001 [95% UI: 0.000;0.016]
+65	0.000 [95% UI: 0.000;0.000]	0.000 [95% UI: 0.000;0.000]	0.000 [95% UI: 0.000;0.000]

Table 12 - Estimated mean exposure to iAs (µg/kg bw/day) through Oatmeal

Age Groups	Both sexes	Male	Female
4-14	0.075 [95% UI: 0.000;0.247]	0.087 [95% UI: 0.00;0.280]	0.059 [95% UI: 0.001;0.191]
15-44	0.036 [95% UI: 0.000;0.120]	0.042 [95% UI: 0.00;0.126]	0.029 [95% UI: 0.001;0.099]
45-64	0.031 [95% UI: 0.000;0.095]	0.031 [95% UI: 0.00;0.098]	0.022 [95% UI: 0.000;0.073]
+65	0.021 [95% UI: 0.000;0.078]	0.025 [95% UI: 0.00;0.079]	0.017 [95% UI: 0.000;0.058]

Table 13- Estimated mean exposure to iAs (µg/kg bw/day) through Cornflakes frosted

Age Groups	Both sexes	Male	Female
4-14	0.008 [95% UI: 0.000;0.063]	0.010 [95% UI: 0.000;0.0671]	0.004 [95% UI: 0.000;0.0398]
15-44	0.001 [95% UI: 0.000;0.0082]	0.001 [95% UI: 0.000;0.0079]	0.001 [95% UI: 0.000;0.0076]
45-64	0.000 [95% UI: 0.000;0.0037]	0.000 [95% UI: 0.000;0.0048]	0.000 [95% UI: 0.000;0.000]
+65	0.000 [95% UI: 0.000;0.0034]	0.000 [95% UI: 0.000;0.003]	0.003 [95% UI: 0.000;0.004]

Table 14 - Estimated mean exposure to iAs (µg/kg bw/day) through Muesli

Age Groups	Both sexes	Male	Female
4-14	0.007 [95% UI: 0.000;0.095]	0.008 [95% UI: 0.000;0.090]	0.007 [95% UI: 0.000;0.067]
15-44	0.007 [95% UI: 0.000;0.045]	0.001 [95% UI: 0.000;0.046]	0.006 [95% UI: 0.000;0.035]
45-64	0.008 [95% UI: 0.000;0.052]	0.010 [95% UI: 0.000;0.056]	0.007 [95% UI: 0.000;0.042]
+65	0.006 [95% UI: 0.000;0.042]	0.006 [95% UI: 0.000;0.042]	0.005 [95% UI: 0.000;0.038]

Table 15 - Estimated mean exposure to iAs (µg/kg bw/day) through Crispbread rye, coarse (Husmans)

Age Groups	Both sexes	Male	Female
4-14	0.000 [95% UI: 0.000;0.004]	0.000 [95% UI: 0.000;0.004]	0.001 [95% UI: 0.000;0.004]
15-44	0.000 [95% UI: 0.000;0.002]	0.000 [95% UI: 0.000;0.001]	0.001 [95% UI: 0.000;0.002]
45-64	0.000 [95% UI: 0.000;0.001]	0.000 [95% UI: 0.000;0.001]	0.000 [95% UI: 0.000;0.001]
+65	0.000 [95% UI: 0.000;0.002]	0.000 [95% UI: 0.000;0.001]	0.001 [95% UI: 0.000;0.002]

Table 16 - Estimated mean exposure to iAs (µg/kg bw/day through Rice Cakes

Age Groups	Both sexes	Male	Female
4-14	0.020 [95% UI: 0.000;0,153]	0.017 [95% UI: 0.000;0.139]	0.024 [95% UI: 0.000;0.152]
15-44	0.002 [95% UI: 0.000;0.028]	0.001 [95% UI: 0.000;0.025]	0.003 [95% UI: 0.000;0.029]
45-64	0.002 [95% UI: 0.000;0.0147]	0.001 [95% UI: 0.000;0.006]	0.002 [95% IC: 0.000;0.025]
+65	0.001 [95% UI: 0.000;0.0057]	0.001 [95% UI: 0.000;0.000]	0.001 [95% UI: 0.000;0.020]